FEBRUARY, 1949

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

SYMPOSIUM ON JAUNDICE

The Clinical and Laboratory Use of Bromsulfalein

The Differential Diagnosis of Jaundice

Medical Therapy in Jaundice

Surgical Therapy in Jaundice

●

Fourteenth Annual Convention

Boston, Mass., 24, 25, 26 October 1949

VOLUME 16 NUMBER 2

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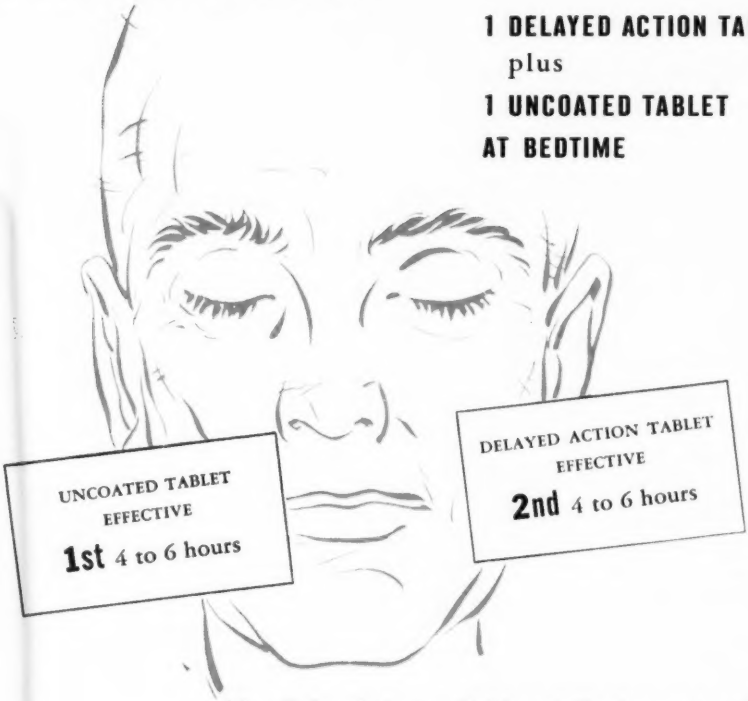

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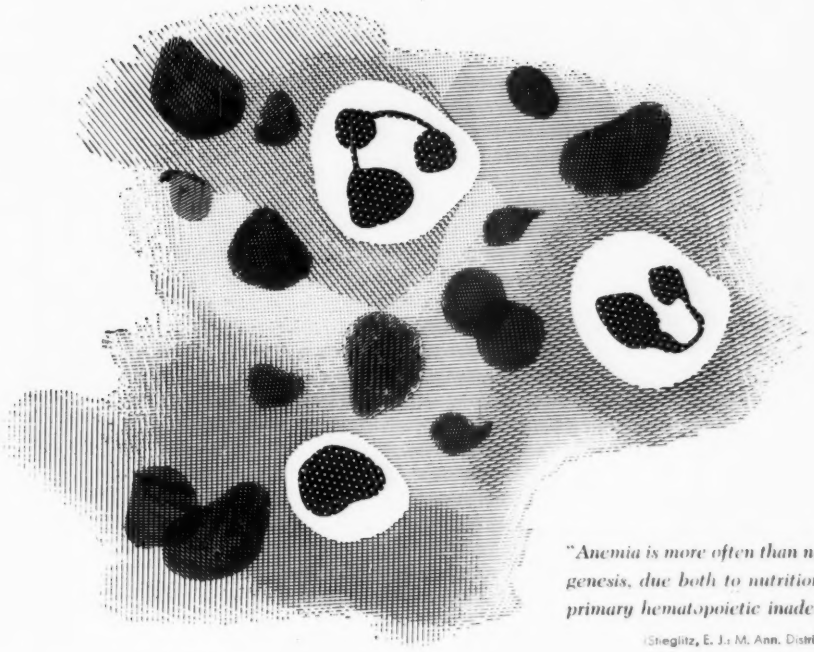

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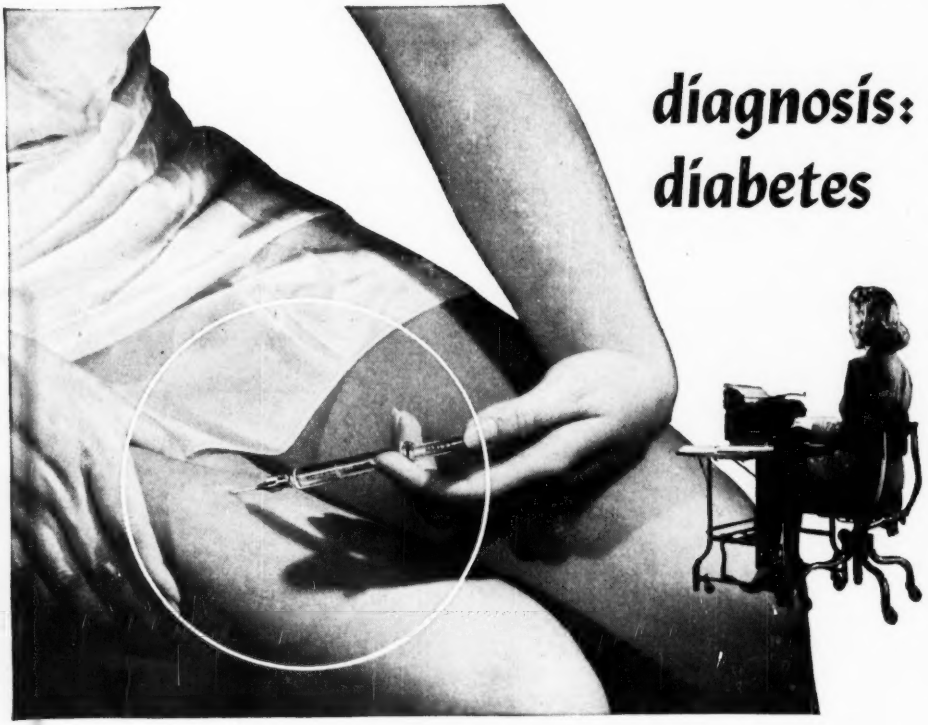

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Volume 16 FEBRUARY, 1949 Number 2

SYMPOSIUM ON JAUNDICE

THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE

RICHARD B. CAPPS, M.D.*†

Chicago, Ill.

In spite of many recent developments in the field of liver disease, the differential diagnosis of jaundice continues to present a difficult and important problem. Although laboratory procedures have been much improved and provide more information than formerly, their very number and complexity often lead to confusion. Thus an accurate and detailed knowledge of the various clinical pictures involved is still essential. Due to the difficulty of presenting a comprehensive review of such an extensive subject in a limited time, I have chosen instead to discuss in detail only those aspects with which I have had the greatest personal experience.

TABLE I

Classification of Jaundice

A. Hemolytic Jaundice
B. Parenchymal Jaundice
  1. Infectious
    Viral hepatitis
    Infectious mononucleosis
    Atypical pneumonia
    Acute brucellosis
    Secondary syphilis
    Malaria
    Spirochetal jaundice
    Yellow fever
  2. Toxic Hepatitis
  3. Cirrhosis
  4. Neoplastic Involvement of the Liver
C. Extrahepatic biliary tract obstruction

For practical purposes cases of jaundice can be divided into three large groups (Table I): namely, those due to hemolysis, those due to parenchymal liver disease, and those due to extrahepatic obstruction of the biliary tract. The first type is rather easily recognized and will not be discussed here. The problem which usually confronts the clinician is that of distinguishing between the other two forms. This

*Read before the Thirteenth Annual Convention of the National Gastroenterological Association, New York, N. Y., 7, 8, 9, 10 June 1948.

†From the Department of Medicine, Northwestern University Medical School and St. Lukes Hospital, Chicago, Illinois.

is of particular importance, because it usually involves the question of surgical intervention. Since most recent investigations have been concerned with jaundice due to parenchymal liver disease or hepatitis, we have chosen to discuss the differential diagnosis of these conditions in detail, and particularly, their differentiation from obstructive jaundice.

Types of Jaundice Due to Parenchymal Liver Disease

By far the most common cause of parenchymal jaundice and the one most likely to cause difficulties in diagnosis is viral hepatitis. Although other infections may produce a somewhat similar picture, notably infectious mononucleosis, acute brucellosis, virus pneumonia, spirochetal jaundice, secondary syphilis and malaria, relatively specific diagnostic procedures are available in each case. Toxic hepatitis is usually associated with a history of chemical exposure. Cirrhosis and neoplastic disease involving the liver must also be considered. Let us first discuss the diagnostic features of viral hepatitis.

Viral Hepatitis

Although there is no specific diagnostic procedure in this disease, there are certain features which have, in our experience, real diagnostic value (Table II).

TABLE II

Diagnostic Clinical Features of Viral Hepatitis

History
1. Exposure
2. Type of onset
3. Prodromal period
4. Relation to exertion

Physical Findings
1. Liver tenderness and type of pain on percussion
2. Tenderness in costovertebral angle
3. Lymphadenopathy and splenomegaly

Course
1. Duration of acholic stools
2. Persistence of symptoms

There may be a history of exposure, consisting in the case of homologous serum hepatitis of the administration of plasma, convalescent serum or whole blood three or four months before the onset of symptoms. Exposure can also occur from any type of parenteral injection, venipuncture or even capillary puncture for blood counts[1]. In the case of infectious hepatitis, exposure includes in addition to the above, ingestion of fecally contaminated food or water so that other cases in the family or the neighborhood are suggestive. The incubation period, however, is only three to six weeks.

The type of onset is often helpful. In homologous serum jaundice it is insidious and not infrequently associated with urticaria, a vesicular eruption, especially on the palms of the hands and arthralgia. In infectious hepatitis the onset is usually acute and febrile for a period of two to four days. This is followed by an afebrile interval of a few days to a week before jaundice appears. Symptoms of lassitude, anorexia, increased flatus, and loose stools are present during this period in both types of the disease. From a diagnostic point of view, a history of such a prodromal or preicteric period is often of considerable value.

Physical examination in acute viral hepatitis reveals several points which may be of diagnostic importance. Liver tenderness is almost always present and usually associated with enlargement. Tenderness is best elicited by direct fist percussion over the right lower thorax. The pain characteristically develops following a short latent period of several seconds, and then gradually increases in intensity for three to five seconds more[2, 3]. An ache usually persists for some time and even until the next day. We have not seen this type of pain with anything except liver pathology. In addition, as we have previously described, in about 50 per cent of the cases there is a small localized tender area in the right costovertebral angle[2]. This is probably produced by that portion of the posterior surface of the liver which is without a peritoneal covering and lies directly on the posterior abdominal wall. In cases where it is difficult to evaluate liver tenderness anteriorly, this sign is very strong evidence that abnormal tenderness is present. Tenderness in the same general region may also be seen in renal disease and in inflammatory conditions of the ascending colon, but these two conditions are readily eliminated and are not associated with anterior liver tenderness. Finally, lymphoadenopathy,

TABLE III

Days After Onset of Symptoms

	61	65	71	75
1 Min.—VDB	3.5		1.7	
Total VDB	6.9		3.4	
Meth. Blue	Pos.	Neg.		Neg.
Strip Test	Pos.	Neg.		Neg.

Case R. V. G.—Convalescent hepatitis—relation of bilirubinuria as measured by the methylene blue and strip test (Watson) to bilirubinemia as measured by Watson's modification of the van den Bergh in mg/100 cc.

especially of the inferior cervical glands is present in over half of the cases and splenomegaly in approximately 20 per cent. Both of these findings are often of considerable value.

One of the most constant features of acute hepatitis is, as we have shown[2, 3, 4], the aggravation by exertion of symptoms and physical findings related to the liver. Although this phenomenon may occur immediately following exercise, the characteristic feature is its persistence for several days or longer. A history of this phenomenon can frequently be obtained. In other cases it may actually occur under the observation of the physician.

Perhaps the most important clinical characteristic of the course of viral hepatitis is the persistence of symptoms and findings. Even though the jaundice may be of very short duration, evidence of active hepatitis as indicated by symptoms and abnormal physical and laboratory findings lasts over a period of weeks. In most cases of hepatitis secondary to other acute infections the course is much shorter. Acholic stools frequently occur in viral hepatitis, but they rarely last for more than one week.

The laboratory findings in acute viral hepatitis are those of an acute parenchymal hepatitis and do not differ from the findings in acute hepatitis from other etiologic agents, except possibly in respect to severity. Evidence of disturbed liver

function is always present in the preicteric stage and is marked by the time jaundice appears. This is an important point in differentiating extra hepatic obstruction. Unfortunately, when the latter has been present for some time, evidence of parenchymal liver disturbance also appears. Thus unless the patient is seen early in the course of the disease the situation may be confusing.

The course of the disturbances in bilirubin excretion is of particular interest[5]. Bile first appears in the urine using Watson's strip test[6] and the methylene blue test[2] prior to detectable elevation of the serum bilirubin level. This is followed shortly by an increase in the prompt direct form of bilirubin in the serum using Watson's technic[7]. At first this may not be associated with a measurable increase in the total serum bilirubin. Finally, both the prompt direct and the indirect forms of bilirubin become elevated in the serum. During convalescence it is noteworthy that the bilirubinuria usually disappears before either form of serum bilirubin reaches normal (Table III). Apparently a renal threshold is developed. This is important because jaundice without bilirubinuria suggests a hemolytic etiology.

Urinary urobilinogen is increased, except during the period of acholic stools. This ordinarily does not last for more than a week. Except in the cholangiolitic form of the disease the serum alkaline phosphatase is only moderately elevated to 10 or 15 Bodansky units, whereas in obstructive jaundice it is much higher.

The evaluation of other liver function tests in regard to differential diagnosis is dependent on their sensitivity and degree of abnormality but just as important on the duration of jaundice. Thus sensitive procedures may become positive after a relatively short period of obstructive jaundice, whereas the less sensitive tests will still be negative. We would like to mention our experience with the hippuric acid test which is rather generally used[2]. In a large series of cases we observed poor correlation between this procedure and the clinical picture. As convalescence progressed the excretion of hippuric acid often fell. Consequently, we studied intensively a group of 156 patients with low hippuric acid outputs, giving 15 grams of glycine simultaneously with the benzoic acid. In only three cases did the excretion of hippuric acid fail to reach normal levels. Casein had a similar, although not as marked, an effect. In both instances about five days were required before the test had returned to the control figure. Similar data have been obtained using the intravenous hippuric acid method. Whether a low output that can be elevated by glycine is an indication of liver dysfunction is not clear. However, it is obvious that the patient's diet for at least five days before the test is most important and that performed in the usual way the test is not reliable.

The blood picture in acute hepatitis is of considerable value. The white count is rarely elevated and usually is low. Immature atypical lymphocytes are present similar to those seen in mononucleosis, but only in small numbers. Anemia is absent except in cases of long duration, and in association with severe liver damage. The sedimentation rate is often normal in the presence of jaundice.

Confusing Clinical Pictures Presented by Viral Hepatitis

We have seen certain clinical pictures in viral hepatitis on a number of occasions which may cause confusion and it is important to recognize them. First, severe abdominal pain may occur during the first week of jaundice. The severity may be sufficient to require morphine. The pain is usually in the right upper quadrant or epigastrium, although it may radiate to the right lower quadrant. Back pain is rare. It is occasionally colicky in nature and may be associated with abdominal muscle spasm. We believe that this pain is due either to sudden increase in liver size with consequent stretching of the capsule or to spasm in the upper portion of the gastrointestinal tract. If clay colored stools are present, such a situation may be confused with a common duct stone. However, the diagnosis can usually be made with considerable certainty by taking a careful history and doing a careful physical examination. In the case of stone there is usually a history of previous attacks of pain or abdominal discomfort with symptom free intervals. In the case of chronic hepatitis with acute icteric exacerbations, symptoms, especially of lassitude, easy fatigue, and right upper quadrant ache aggravated by exercise, have been present between bouts. When jaundice is mild and clay colored stools absent, the pain may be mistaken for acute pancreatitis or a ruptured viscus. The demonstration of an enlarged tender liver as well as the presence of significant jaundice and a leucopenia, is usually adequate to establish the diagnosis.

The second confusing picture is that of the case of chronic viral hepatitis with persistent jaundice and often light colored stools over a period of months. This condition which has been called cholangiolitic hepatitis by Watson[8] has been recognized for a number of years in its later stages under the names of biliary and Hanot's cirrhosis[9]. In 1940 Hanger[10] described the occurrence of such cases in a luetic clinic following the first few injections of neoarsphenamine. In his cases the cephalin cholesterol flocculation test was negative, the jaundice was persistent and biopsy showed presence of multiple bile thrombi in the smaller bile canaliculi. Although Hanger attributed the jaundice to these bile thrombi, other authors, notably Watson, feel that they are simply incidental and that the jaundice is the result of injury to the smaller bile ducts themselves.

In the Mediterranean Theatre of Operations we had the opportunity of studying twenty-one cases of syphilis associated with infectious hepatitis who were receiving mepharsen. In 16 cases the hepatitis ran the usual course and was apparently unaffected by continued mepharsen treatment. In the other 6 cases, however, jaundice had developed after the 3rd to 9th treatment and the patients presented the clinical picture described by Hanger. The cephalin cholesterol flocculation was uniformly negative and the serum alkaline phosphatase markedly elevated. When such cases have acholic stools, diagnosis is difficult. Other tests of liver function are occasionally abnormal including the serum globulin.

Recovery may take place after a relatively prolonged period of jaundice or chronic hepatitis and cirrhosis may develop. Recently we have observed 5 such cases. In every instance surgery had been performed or was contemplated because

of the suspicion of extra hepatic obstruction. Late cases, however, can often be recognized clinically because of the deep jaundice with only partially acholic stools, the frequent splenomegaly and spider angiomata and the laboratory evidence of profound liver dysfunction. A low serum albumin level is especially significant. Exploration under general anesthesia is naturally not desirable.

As we have previously pointed out[3, 11], the Graham-Cole test may give an absent gallbladder shadow in the presence of severe liver disease. Low grade jaundice does not of itself prevent a normal gallbladder visualization. This must be borne in mind in cases of mild jaundice with a nonfilling gallbladder. In our experience this test is not interfered with unless liver injury is pronounced and usually in the presence of definite liver tenderness and enlargement.

According to such data as is available in the literature between 20 and 25 per cent of the patients who have clinically recovered from acute viral hepatitis, have a residual elevation in their serum bilirubin[12]. Where this has been measured by the Van den Bergh method it has been found to be entirely of an indirect or retention type. We have seen a number of such cases who habitually carry from three to five milligrams of bilirubin in their serum. This must not be confused with other types of retention jaundice. The history and other laboratory evidence of liver dysfunction serve to establish the diagnosis. However, it may be necessary to employ a number of the more sensitive procedures to demonstrate the presence of liver injury.

Other Types of Parenchymal Jaundice

Although it is probable that many acute infections are associated with a certain amount of liver injury, in most instances the damage is transitory. In certain specific conditions, however, we have observed a hepatitis which is extremely similar to that seen in viral hepatitis. Infectious mononucleosis is perhaps the outstanding example. The blood picture, heterophile agglutination and marked generalized adenopathy, if present, serve to make the diagnosis. We have frequently observed a form of hepatitis, indistinguishable from viral hepatitis, to follow virus pneumonia. That this is not a coincidence was shown by routine liver function tests performed on a series of 70 consecutive cases of viral pneumonia. The cephalin cholesterol flocculation test was 2+ or more in 24 hours in 60 per cent and the bromsulfalein was over 8 per cent in 45 minutes in over 30 per cent. The recognition of this condition is dependent upon a characteristic pulmonary lesion. Spirochetal jaundice is not often seen in this country. The white count is usually elevated, and the patients are sicker than in viral hepatitis. In addition, the temperature tends to remain high for a considerably longer period of time. The hepatitis associated with secondary syphilis is characterized by a positive Wassermann, and usually by a luetic rash. Malaria may occasionally produce a confusing picture, but the presence of splenomegaly, anemia, a rapid sedimentation rate, and usually a characteristic temperature curve are of diagnostic value.

Toxic hepatitis must usually be diagnosed on the basis of a history of chemical exposure. Fever is essentially absent. In the case of carbon tetrachloride poisoning,

oliguria, anuria, and hypertension are frequently observed. Clay colored stools are only occasionally seen. The presence of anemia or other evidence of bone marrow damage is always suggestive.

Cirrhosis of the liver with jaundice should not often cause diagnostic difficulties. In addition to the frequent presence of an enlarged spleen and spider angiomata, liver function tests reveal profound abnormalities. Perhaps the most important finding is a hypoalbuminemia.

Finally, we must mention the jaundice that is seen with primary or secondary neoplastic invasion of the liver. If the common duct is occluded, the stools may be clay colored. In general, such cases are characterized by a progressive course and anemia is almost always present. Liver function tests may indicate parenchymal damage.

Certain Newer Diagnostic Procedures

In spite of the most intensive clinical and laboratory study, we are still unable to establish the diagnosis with certainty in a number of cases. Where the differential diagnosis involves the question of surgery, a correct diagnosis is obviously of the greatest importance to the patient. Surgical procedures in the presence of acute hepatitis may produce a fatal outcome. Nevertheless, we are often forced to explore the belly in order to make a diagnosis. The diagnosis in many of these cases can be settled by liver biopsy. Needle biopsy probably has an overall fatality rate of between one and two per cent, although this varies in different hands. Certainly we are often justified in accepting this risk in order to establish the diagnosis. Peritoneoscopy, on the other hand, is probably safer, and at the same time provides considerably more information. In the hands of an experienced operator, the diagnosis is often clear from the gross observation of the viscera. Dr. Horan of Detroit, for example, at the last count had done some 1,900 examinations with only one fatality and that a questionable one. The difficulty with this type of procedure is that trained observers are very scarce. Finally a biopsy is readily and safely obtained by a surgeon through a small right upper quadrant incision under local anesthesia. Except for the economic and psychologic aspects, we believe that this method is distinctly preferable to the needle.

One other new diagnostic procedure should be mentioned, recently reported by Royer and Solari[13] and which has been performed by Horan for the last four or five years. This consists of the injection by needle into the gallbladder of an opaque dye while the gallbladder is under direct vision of the peritoneoscope. In this manner, it is possible to visualize the gallbladder in cases of jaundice when the viscus cannot be seen by ordinary methods. Apparently there is little attendant risk.

In conclusion I have tried to point out some of the more significant diagnostic features of the various types of parenchymal liver disease associated with jaundice. A thorough knowledge and understanding of these conditions should serve to clarify the diagnosis in many cases that are otherwise obscure. The apparent recent increase in incidence of these conditions makes this the more important.

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THE CLINICAL AND LABORATORY USE OF BROMSULFALEIN*†

C. WILMER WIRTS, M.D.
Philadelphia, Pa.

Since the introduction of the halogenated phthaleins into the clinical and experimental investigation of hepatic function[1, 2], a variety of methods have been proposed for estimating the capacity of the liver for eliminating these substances. Originally, the quantity of dye (phenoltetrachlorphthalein) excreted in the feces was estimated[1, 3, 4, 5], but the obvious technical difficulties inherent in this procedure rendered the results of doubtful value. With the introduction of the procedure of biliary drainage, duodenal intubation attempts were made to evaluate the state of hepatic function by determining (a) the time of appearance of the dye in bile obtained by this means and (b) the total quantity eliminated in the bile during varying periods of study[3, 6, 7, 8]. However, the relative crudity of

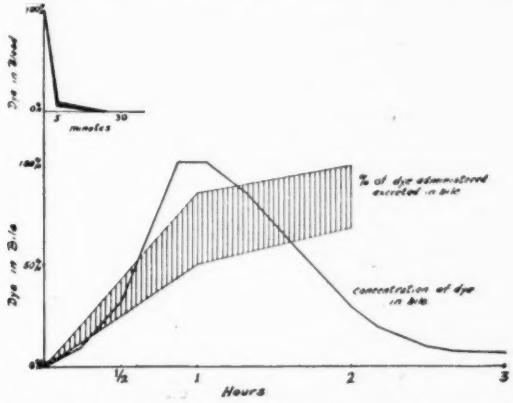

Fig. 1—Schematic representation of time relationships of removal of bromsulfalein from the blood and excretion in the bile.

methods then available made accurate quantitative estimation of the dye virtually impossible. Since the introduction in 1925 by Rosenthal and White[9] of determining the retention of bromsulfalein in the serum or plasma all other methods previously employed have been discarded. This test has proved to be of great practical clinical value but in spite of its widespread use, until recently there was no exact knowledge of the mechanism of the removal of bromsulfalein from the body.

On the basis of simultaneous study of the concentration of intravenously injected bromsulfalein in the blood and bile of chronic bile-fistula dogs, cholecystectomised T-tube patients and normal unoperated patients we have demonstrated

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†From the Department of Medicine and the Gastrointestinal Clinic, Jefferson Medical College and Hospital, Philadelphia, Pennsylvania.

the following facts connected with the mechanism of excretion of this dye. In normal subjects, following intravenous injection of 2.0 mg. of bromsulfalein per kilogram of body weight, the dye is removed from the blood very rapidly (85-95 per cent in five minutes and 100 per cent in thirty minutes). It appears in the bile usually, but not invariably, during the first fifteen minutes and attains a maximum concentration in forty-five to seventy-five minutes, falling subsequently to a relatively low level at two hours, but not often disappearing completely for five to six hours; 50 to 83 per cent of the quantity injected is excreted in the first hour and 67 to 100 per cent in the first two hours. Reference to Figure 1 shows these data in graphic form.

Abnormal excretion of the bromsulfalein in the bile was evidenced by one or more of the following phenomena: delayed appearance of the dye in the bile; delayed attainment of maximum concentration; prolonged high curve of excretion; subnormal concentration (flat type of curve); abnormally low total excretion in one or two hours after injection[10, 11, 12].

Additional studies on unanesthetized, chronic bile-fistula dogs with normal liver function[13] shows that choleresis following administration of certain bile salts (sodium dehydrocholate) is accompanied by an increase in serum bilirubin concentration, delayed removal of bromsulfalein from the blood and a diminished rate of excretion of bromsulfalein in the bile. When severe impairment of liver function is produced in these dogs by carbon tetrachloride, the sodium dehydrocholate produced moderate choleresis but had no significant influence upon the level of serum bilirubin, the degree of retention of bromsulfalein in the blood or the rate of excretion of dye in the bile. In the presence of partial bile stasis, administration of sodium dehydrocholate was followed by moderate choleresis, increase in serum bilirubin concentration and delayed removal of bromsulfalein from the blood, but, in sharp contrast to the findings in normal animals, there was a simultaneous increase in the rate of excretion of dye in the bile. The reason for these divergent findings may be due merely to a difference in the severity of hepatocellular damage, but it may possibly be related to the occurrence of impairment of Kupffer cells in addition to that of polygonal cells in carbon tetrachloride poisoning.

We have also shown that the intravenous injection of India ink in bile-fistula dogs[13] is followed by an increase in serum bilirubin concentration, delayed removal of bromsulfalein from the blood and diminished rate of excretion of dye in the bile with no significant influence on bile volume. This is in agreement with the findings of other investigators which suggest that the cells of the reticuloendothelial system may play an important part in the removal of halogenated pthaleins from the blood stream.

From all these data it is felt that two separate or related mechanisms are involved in the removal of dye from the body. There is some evidence that the first (rapid removal from the blood), is related to the reticuloendothelial cell activity, perhaps largely to that of the Kupffer cells. There seems to be little doubt that the second, (the more gradual process of the excretion of dye in the bile), is

a function of the polygonal cells of the liver. A striking example of the dissociation of the two phases of this mechanism is illustrated in Figure 2. These data were obtained in consecutive studies in a bile-fistula dog during a period of increasing bile stasis. Curve 1 is essentially normal, as is the total dye excretion at that time. Curves 2, 3, and 4 became progressively abnormal with corresponding progressive decrease in the total dye excretion. At no time was there abnormal retention of dye in the blood. These findings suggest that during the early period of bile stasis the obstruction to the flow of bile may interfere with the excretion of the dye by the hepatic cells for a considerable period of time before the capacity of the liver (Kupffer cells?) for removing the dye from the blood is impaired.

On the basis of continuous intravenous injection studies of bilirubin and bromsulfalein separately, it has been determined that these two substances prob-

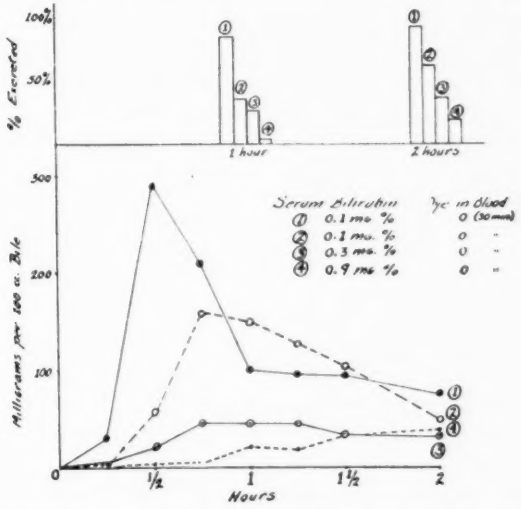

Fig. 2—Increasing abnormality of bromsulfalein excretion with no retention in blood during period of progressive obstruction of common bile duct in dog.

ably are excreted by the same mechanism, but, when injected simultaneously, bromsulfalein is excreted in the bile preferentially[14].

In our experience the simultaneous study of the concentration in blood and bile of intravenously injected bromsulfalein is of considerable clinical value. This study can be done by establishing a free flow of bile in the usual manner employed in performing duodenal biliary drainage; bromsulfalein is then injected intravenously and a blood sample taken at the end of thirty minutes. Bile is collected in fifteen minute fractions, the concentration of dye determined, and the total quantity excreted over a two-hour period calculated. Normally, as previously mentioned, there should be no retention of dye in the blood after thirty minutes and most of the dye should be excreted in the bile during the first hour.

Because of the difficulty experienced in interpreting the results of routine liver function studies in a group of posthepatitis patients it was decided to employ this biliary bromsulfalein test[15]. Twenty-five patients were selected because, in spite of continuous treatment for one or two months following an attack of infectious hepatitis or serum jaundice and the complete disappearance of icterus of skin and sclera, they were still suspected of having some impairment of liver function.

The patients were divided into four groups on the basis of the following criteria: (1) *prolonged persistence of symptoms* with normal physical findings and normal routine liver function studies; (2) *prolonged abnormal physical findings* without accompanying symptoms and with normal routine liver function studies; (3) *prolonged abnormal routine liver* function studies without symptoms or abnormal physical findings and (4) *prolonged abnormal routine liver function studies and physical findings* without symptoms.

Initially all twenty-five patients showed an abnormal response to the biliary bromsulfalein test. However, after one or two months additional treatment sixty per cent showed gradual improvement until the response finally approximated normal. While some improvement was noted in the remaining forty per cent they continued to show an abnormal response in spite of one or two months additional treatment.

From the study of these patients it is felt that the biliary bromsulfalein test is of practical help in evaluating minimal or questionable hepatic functional impairment.

Summary

The practical application of studying the removal of bromsulfalein from the blood as a test of liver function developed much more rapidly than the knowledge of the actual mechanism involved. While the exact method of the removal of the dye from the body is not established it would appear, on the basis of experimental and clinical data, that excretion is probably dependent upon a dual mechanism; (1) rapid removal of dye from the blood by the Kupffer cells of the liver and (2) the slower excretion into the bile by the hepatic polygonal cells (greatest percentage within one hour). Evidence is also available suggesting that if the liver is the only organ removing bromsulfalein from the blood it must represent the temporary storage place wherein the dye resides during the interval between its removal from the blood and its total excretion in the bile. Bilirubin and bromsulfalein appear to be excreted by the same mechanism, but when injected simultaneously, bromsulfalein is excreted in the bile preferentially.

The biliary bromsulfalein test which has been useful in evaluating liver function in selected patients is based on the clinical application of these principles.

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MEDICAL THERAPY IN JAUNDICE*

I. R. JANKELSON, M.D.†
and
LEO R. MILNER, M.D.**
Boston, Mass.

Introduction

A prerequisite for the proper management of a jaundiced patient is a correct diagnosis of its pathogenesis. Jaundice may be the presenting symptom and the most important sign of a diseased state, which requires active medical or surgical treatment. On the other hand, it occurs as an incidental finding, and from the point of view of therapy as a relatively unimportant complication.

When a jaundiced patient is first seen only too often a definitive diagnosis is impossible. In such cases careful clinical observation and intensive laboratory studies are required for several days to several weeks. During this period of study, medical management should be instituted. Depending upon the proper classification of the individual case, the medical treatment must be continued or surgery should be resorted to if and when indicated.

Classification of Jaundice

For the purposes of this presentation we choose to classify jaundice as (1) prehepatic (2) hepatocellular and (3) posthepatic. We are fully aware that this is somewhat arbitrary, since mixed forms are frequent. But no other classification so far proposed is faultless in this respect. From the therapeutic point of view we find the above division of jaundice to be simple and indicative of the proper approach to treatment.

By and large, one can state that the prehepatic jaundice does not require liver management. The underlying condition, namely hemolysis, must be properly treated and with its improvement or cure, the jaundice usually subsides.

The hepatocellular jaundice is primarily a problem of medical management of either acute or chronic liver disease and as such is the major and most important part of this contribution. It will be discussed below.

The posthepatic jaundice is mainly a surgical condition and the medical treatment of it is chiefly concerned with pre- and postoperative management in which the surgeon and internist should closely cooperate.

Treatment of Jaundice of Undetermined Etiology

As mentioned above, patients while observed for proper classification should be treated medically. They should be at bed rest, preferably in a properly equipped hospital where intensive liver studies can be carried out. Their food intake must be

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†Assistant Professor of Medicine, Tufts College Medical School, Junior Visiting Physician, Boston City Hospital.
**Assistant in Medicine, Beth Israel Hospital, Boston, Mass.

adequate and should be supplied orally by preference and parenterally only if necessary. Their protein supply should be sufficient to keep them in a nitrogen balance. However, in instances where a hypoproteinemia, with or without a reversed albumin-globulin ratio is present, higher amounts of proteins are indicated. If a patient cannot partake orally of an adequate amount of properly balanced proteins of high nutritive value he should be given supplementary parenteral amino acids, blood plasma, human albumin or blood transfusions (if anemia is also present) to restore the deficiency. It is generally accepted that a low fat diet is indicated in jaundiced patients. However, recently the observations of Hoagland et al.[1a] and Wilson et al.[1b] seem to indicate that larger quantities of fat may be harmless or even advantageous. Carbohydrates should be administered in large quantities first to supply a satisfactory caloric intake and secondly to increase the glycogenesis of the liver. Only if sufficient carbohydrates cannot be taken by mouth must one resort to intravenous glucose therapy. Having had some experience with insulin treatment of jaundice[2] and being cognizant of many contributions on this subject, particularly from older European clinicians[3], we are not overly impressed with its value and do not employ it except when diabetes mellitus with or without hemachromatosis is present. When vitamin deficiencies are recognized or even suspected large doses of vitamins should be administered by mouth or parenterally. This applies particularly to Vitamin K and especially in the patients who are likely to have surgery on the biliary tract. In the presence of an anemia this should be properly treated by liver extract, iron or blood transfusions depending upon its type, severity and response to medication. The water metabolism is often disturbed in liver disease[4]. With it there may be changes in the electrolytes. Unless there is edema or ascites 2,000 to 3,000 cc. of fluid should be given daily to a jaundiced patient by mouth if possible, otherwise parenterally as glucose solution in water or saline to which amino acids and vitamins can be added as needed. Saline should not be used if edema or ascites are present. While discussing water metabolism we wish to emphasize the good omen of *spontaneous* diuresis.

Transduodenal bile drainage is indicated in many cases as part of the diagnostic work up, but in our opinion is rarely if ever useful in the treatment of undiagnosed jaundice. Neither do we approve of the administration of bile salts except in relation to the oral use of Vitamin K. One should abstain from drastic cathartics and purgatives, but an occasional dose of calomel, sodium phosphate or sodium sulfate is useful in the control of constipation. If severe pain or colic are present this must be controlled by opiates, demerol or barbiturates. Nitroglycerine and amyl nitrite in our experience often fail to control pain.

The treatment of pruritus, which often is most distressing to the patient, should be mentioned. There is no specific remedy for it except the cure of the underlying disease. Palliative treatment consists of generous application of white wash, calomine wash and the use of starch or oatmeal baths. Calcium gluconate is recommended but is of questionable value. The subcutaneous or oral administration of ergotamine tartrate in our hands has often failed to give even temporary relief and may be dangerous[5]. Opiates and barbiturates should be employed sparingly

and cautiously, since in the presence of serious liver disease they may not be properly detoxicated.

Treatment of Prehepatic Jaundice

It is difficult to conceive even mild jaundice caused entirely by increased hemolysis. According to Fox and Ottenberg[6] the normal liver excretes each day the bilirubin derived from the destruction of 12.5 gm. of hemoglobin and can eliminate much more. Rich[7] believes that the jaundice is not due to overproduction of bilirubin alone, but the blood destruction and the resulting anemia cause anoxemia of the liver with a corresponding curtailment of bile excretion. Nevertheless, from the clinical point of view and surely as far as its management is concerned, the hemolysis of whatever cause is the focal point.

The causes of prehepatic jaundice are many. They can be classified as various forms of anemia, febrile diseases, hemolysins of the immune body type, bacterial toxins and chemical or animal poisons. The course of the hemolysis may be acute, chronic or recurrent and the jaundice varies accordingly.

The treatment depends upon the underlying cause and hence varies a great deal. As examples of various approaches to the problems involved, one may mention liver therapy in pernicious anemia, splenectomy and/or blood transfusions in congenital or acquired hemolytic jaundice, quinine in jaundice accompanying malaria, antibiotics in pneumonia, dicumarol or heparin in pulmonary embolism, etc. The most serious therapeutic problem in this group of cases is the jaundice following mismatched blood transfusions[8]. Unfortunately, no specific treatment is available for either this type of jaundice or the other even more serious manifestations of such accidents. Erythroblastosis fetalis should also be considered here and the most recent management of this disease by total or subtotal replacement of blood should be mentioned[9].

Treatment of Hepatocellular Jaundice

We will discuss the treatment of several well defined diseases in which the primary disturbance consists of either acute or chronic liver cell damage. Included in this group are infectious hepatitis, homologous serum hepatitis, acute and subacute yellow atrophy, toxic hepatitis, Weil's disease, amebic hepatitis and cirrhosis of the liver. All these diseases have one common denominator, namely liver cell injury, which varies in degree, in acuteness, in the amount of spontaneous degeneration and response to proper and adequate treatment. The management is primarily medical, surgery is employed but rarely for complications and alleviation of mechanical difficulties as, for instance, portocaval anastomosis in portal cirrhosis of the liver. For lack of space and because of other considerations we will not discuss primary and secondary malignancies and luetic liver involvement. Jaundice in these diseases, although a common symptom, from the therapeutic point of view is unimportant except in that it often is accompanied by severe and intractable pruritus. The medical management of pruritus was described above.

Infectious hepatitis is a self-limited disease, occurring in epidemics and as sporadic cases. It is now generally accepted that this disease as well as the related but not identical homologous serum jaundice are caused by a filtrable virus or viruses. In infectious hepatitis the virus is transmitted by food, water, feces, flies, fingers and possibly but not probably by droplet infection[10]. Therefore, prevention of at least the epidemic form is dependent upon good hygiene, proper sanitation, personal cleanliness and avoidance of exposure to the causative agent. Intramuscular human gamma globulin[11] given to exposed susceptible subjects before the development of prodromal symptoms, often prevents an attack of the disease or at least attenuates it. Since the disease is most common in young adults and children, such persons, when exposed should be routinely inoculated. In our opinion, patients with this disease should not be kept in an open ward. We saw on one occasion an interne and on another an undergraduate nurse develop an infectious hepatitis contracted from a patient with a sporadic case. Precautions should be taken very similar to those exercised in the management of typhoid fever patients, namely screening the patient, marking dishes and silverware, disposal of excreta, etc. Here one should mention that ordinary chlorination of water does not kill the virus of infectious hepatitis and probably not that of homologous serum hepatitis[12]. Isolation is not necessary in homologous serum hepatitis. Gamma globulin is of doubtful value in preventing this disease[13]. Careful selection of blood donors, eliminating people with enlarged livers or spleens, those who have had a hepatitis within six months and those who have recently been exposed to this disease is important in the prevention of homologous serum hepatitis. In pooled liquid, dehydrated or frozen plasma smaller pools reduce the incidence of it. Thorough sterilization of needles and syringes must be carried out. Recently there appeared a report that serum exposed to ultraviolet rays is less likely to cause a hepatitis[14].

Although both diseases are usually self-limited, some patients develop a chronic hepatitis, while others an acute or subacute yellow atrophy. Whether the usual form of hepatitis ever terminates in an atrophic cirrhosis is questionable, but the less frequent forms of cholangiolitic or pericholangiolitic hepatitis at times results in a cholangiolitic cirrhosis[15] (Hanot's cirrhosis?).

There is no specific therapy for either infectious or homologous serum hepatitis. The crux of the treatment is bed rest and diet. In severe cases the bed rest should be absolute until the jaundice and the liver tenderness as determined by palpation and fist percussion disappear. In milder cases semiambulatory management, permitting bathroom privileges, may suffice and many cases may be treated at home. However, even in such mild cases all work must be prohibited. Early ambulation in the severe instances and early resumption of normal activity in the milder ones predispose to recurrences and the development of chronic hepatitis either with or without jaundice, often leading to prolonged invalidism. Hence, one should rather err in insisting upon longer rest, than allow activities too early.

The diet should be adequate in calories to prevent weight loss. The foods allowed should include 350 or more gm. of carbohydrates and 75 to 125 gm. of protein. It is generally assumed that fats are injurious and should not be given to

patients with hepatitis. However, a diet without some fats is unappetizing. Inasmuch as anorexia is a very common symptom of this disease, it often becomes difficult for the patients to ingest sufficient food. Small amount of fats (50-75 gm.) per diem can be safely given and larger quantities probably do no harm[1a]. Only if the patient refuses adequate food or if vomiting is marked is there need for intravenous alimentation, which should consist of amino acids or plasma, glucose and saline.

When an acute or subacute yellow atrophy is present or even suspected, supplementary intravenous feedings should be instituted and persistently carried out.

Medicinal treatment is of no value in hepatitis. Penicillin and streptomycin are valueless and sulfa compounds may be dangerous. Neither methionine nor choline and cystine in our experience are of use in acute cases. In a small group of chronic hepatitis cases we are impressed by the value of methionine; however, the number of cases observed is too small to be conclusive. We have had no experience with choline and cystine in acute or chronic hepatitis. Wilson[1b] reported on the use of cystine in acute hepatitis and claims favorable results under controlled conditions.

In chronic hepatitis a similar regime must be carried out, but due consideration must be given possible deficiency states which may develop. Therefore, vitamins and iron must be given where indicated. Intramuscular crude liver is an important adjunct in the treatment of these cases.

In the Boston City Hospital we have for several years used the White's mixture for supplementary oral feedings.

Its formula is as follows:

100 gm. skimmed powdered milk
40 gm. sugar
750 cc. skimmed milk
Vanilla to taste

Toxic hepatitis occurs in various forms of poisoning. Some are largely industrial in origin, like in carbontetrachloride, tetrachlorethane or phosphorus. Others are the result of medication as seen in arsenic, chloroform or cinchophen. While in a third group it may be accidental such as mushroom poisoning or phosphorus. The degree of susceptibility to toxic liver substances, as for instance carbontetrachloride, varies a great deal. We are rather impressed that the determining factor is the antecedent status of the liver, in many cases dependent upon the nutritional state of the person. Preventive measures in industrial poisoning are primarily connected with engineering problems, which we will not discuss here.

Among the drugs arsenic and cinchophen are the chief offenders, less frequently carbontetrachloride employed medicinally and rarely chloroform. While administering these drugs one must be on the lookout for possible liver damage and be prepared to discontinue the drug whenever clinical or laboratory evidence of liver dysfunction is noted. Preventive measures in accidental poisonings are applicable mainly to mushrooms. Only the known nonpoisonous varieties should be eaten.

The treatment of toxic hepatitis varies with the circumstances. In industrial poisonings the patient should be removed from the source of the poison or if

need be, change his occupation. Otherwise, the treatment is symptomatic. Rest is important. The diet should be a high carbohydrate, high protein and low fat as outlined above for infectious hepatitis. If an atrophic cirrhosis develops, as we have repeatedly seen, the management must be identical with that of Laennec's cirrhosis, which will be discussed below. Acute and subacute yellow atrophy are relatively rare complications.

Arsenical poisoning in our experience, based on experimental work, responds well to intravenous administration of sodium dehydrocholate. Sodium thiosulfate is another drug frequently used but according to Appel and Jankelson is less efficacious than sodium dehydrocholate[16]. Bal[17] has been used recently with excellent results. No specific treatment is available in cinchophen poisoning[18] and symptomatic management is the usual method. However, frequent instances of acute and subacute yellow atrophy have been reported. Here, too, the preceding nutritional state of the patient probably is important. Methionine as an adjunct in the treatment of toxic hepatitis is probably of some value and should be tried.

In mushroom poisoning brisk laxatives and emetics are indicated to evacuate the digestive tract of poisons still present. To combat dehydration intravenous administration of glucose in saline should be given as needed. If symptoms of vascular collapse are present the usual supportive measures should be employed. We have had no experience with use of an antitoxic serum advocated by Dujarric de La Riviere[19].

Weil's disease is rare in this country. However, spontaneous cases are seen, usually as a result of occupational exposure to rat infested surroundings. There are several European reports of the use of immune horse or goat serum in prevention and cure of this disease[20]. As yet such serum is not available here. In two instances we have used human serum obtained from a patient who recently recovered from an attack of this disease with very gratifying results. Arsenicals and bismuth salts have been tried in the treatment of this ailment. More recently penicillin[21] is used in large doses with apparently good results if given early in the disease. The symptomatic treatment is identical with that of infectious hepatitis.

Amebic hepatitis:—Jaundice occurs in only a small per cent of amebic hepatitis. When the diagnosis is made, approved antiamebic treatment should be employed. The combined treatment, consisting of intramuscular administration of emetine hydrochloride and the oral use of the arsenical or iodine antiamebic drugs, as carbarsone, diodoquin or vioform is best[22]. The danger of peripheral neuritis and myocardial degeneration, the result of toxic doses of emetine, must be borne in mind. No more than 0.500 to 0.650 gm. of emetine should be given to any patient in one course. Arsenical dermatitis and iodine sensitivity also occur. After 7 to 10 days of the combined treatment, the oral drugs should be continued in the following dosages. Carbarsone 0.500 to 0.750 gm. daily for 10 days. Then after a rest period it may be repeated or another drug employed such as vioform 1.5 gm. daily can be used for 10 days or as an alternate diodoquin 1.89 gm. daily for seven days. If an abscess is present it may be evacuated by needle if accessible or require surgery.

Yellow fever:—One of the greatest accomplishments of preventive medicine is the control of yellow fever. It is a proud chapter in medical history well known to all physicians and many laymen. At this time there is no need to recapitulate it. During the second world war phophylactic inoculations with yellow fever vaccine, in which human serum was used in preparation was widely practised and resulted in prevention of this disease in the armed forces. In the early stages of these mass inoculations many cases of homologous serum hepatitis developed[23]. In fact, they were the first cases of this type of hepatitis carefully studied and described.

Once the disease develops there is no specific treatment and the management is symptomatic.

Cirrhosis of the Liver:—Jaundice occurs at some time during the course of Laennec's cirrhosis in approximately 50 per cent of the cases. Although spontaneous disappearance of icterus occurs, it is likely to persist or recur. It indicates persistent or recurrent liver cell injury. Although cirrhosis of the liver is a very chronic disease, it should not be considered as a static one; and during exacerbations jaundice is likely to develop or increase in intensity, while in remissions it may disappear. Thus, increasing or persistent jaundice tends to make the prognosis poor.

The prevention of an atrophic cirrhosis of the liver is intimately connected with a proper diet. Alcohol, long considered the chief offender, is only a contributory factor, though often an important one. The strongly alcoholic patient is more likely to be on an inadequate diet and hence develop an alcoholic cirrhosis[24]. Moreover, a large intake of alcohol, despite a proper diet, predisposes to fatty infiltration of the liver, which although reversible, may be the initial stage of fibrosis. Absolute or relative deficiency in thiamine chloride and probably other fractions of Vitamin B is considered an important factor in the development of this disease. With the ingestion of large quantities of alcohol, larger quantities of this vitamin become necessary. In alcoholics, mild hepatotoxic substances cause greater liver damage than ordinarily and, therefore, may produce a cirrhosis. Hence, both in the prevention and treatment of a cirrhosis, alcohol should be interdicted. A well balanced diet, adequate in calories, protein and vitamins is the best preventive measure in cirrhosis of the liver.

The treatment of jaundice in a cirrhosis of the liver is closely associated with the management of this disease and does not require special consideration. The modern therapy has resulted in increased longevity of cirrhotic patients and restitution of a greater number to useful activity and self support[25]. This is particularly true when the diagnosis is made early and proper therapy instituted in that stage.

The management is largely dietetic. Patek[26] and Patek and Post[27] emphasized the great benefits to be derived from a high protein diet. Since then, increasingly higher amounts of protein are given to these patients. The diet should contain 3,000 or more calories per day and include 125 to 200 gm. of protein, 350 or more gm. of carbohydrates and from 50 to 175 gm. of fats. The food should be in an easily digestible form. The best sources of protein are meat, egg white, milk and low fat cheese. The latter two are particularly stressed as a good source of methionine,

the value of which will be discussed below. Carbohydrates in the form of cooked or raw vegetables and fruits, sugar, bread, sweetened fruit juices and jams should be eaten in large portions. Vegetable fats, butter and cream are better tolerated than animal fats. There is experimental evidence that unsaturated fats are better utilized than the saturated ones[29], also that the fatty acids with less than 12 carbon atoms are more readily metabolized and less likely to produce fatty infiltration of the liver[30].

If the patient cannot eat sufficient food, supplementary alimentation by intravenous route should be given. Blood plasma and amino acids are indicated when a hypoproteinemia is present. Glucose in 5 or 10 per cent solution in saline, or if ascites is present, in sterile water can be given daily in from 1,800 to 3,000 cc. Liberal to large amounts of the B-complex vitamins are a major adjunct to the dietary management. It can be administered as Brewer's yeast up to 25-45 gm. daily, possibly reinforced with thiamine chloride in 5 to 15 mg. doses. Vitamin A deficiency is likewise frequently present and should be combated by large doses of this vitamin. Vitamin K, to avoid hypoprothrombinemia, can be given orally or parenterally. Multivitamins given by mouth are of value. Crude liver extract in 3 to 5 cc. doses, intramuscularly, should be given 3 to 4 times a week in the treatment of liver cirrhosis. We have no experience with the intravenous administration of a specially prepared liver extract, but know of some very favorable reports of its use[31], as well as about severe reactions[24].

Methionine as well as choline and cystine are definitely lipotropic amino acids[32] and as such have been tried in the treatment of cirrhosis of the liver in men and in prevention and treatment of experimentally produced cirrhosis in animals. The experimental work appears quite conclusive that methionine in proper doses prevents the development of fatty infiltration of the liver[33]. So do choline and cystine when used together[33]. Excess of cystine or insufficient methionine[34] produce a fatty liver or cirrhosis with necrosis. In artificially induced fatty livers the process can be reversed by proper administration of methionine or choline and cystine[34].

The evidence of their value in human cirrhosis is neither extensive nor conclusive. Russakoff and Blumberg[35], Beams[36], Cayer[28] and Morrison[24] reported satisfactory improvements from the use of methionine or choline and cystine with the former more effective than the latter two. According to Gyorgy[33c] casein and egg white are rich in methionine and therefore should be given in large quantities in this disease. Methionine in 3-5 gm. and choline and cystine in 2-4 gm. each, daily, can be used as supplements in the treatment of human cirrhosis. Our own impression is that the best results are obtained in fatty infiltrated livers, while in advanced fibrosis they are less efficacious.

In a disease as chronic as cirrhosis of the liver perseverance of treatment must be emphasized and spectacular early results should not be expected. Generally speaking we are convinced that the cirrhotic patient who eats well does better than the one who does not take all the food offered to him.

Posthepatic Jaundice:—Posthepatic jaundice, acute or chronic, persistent or intermittent, totally obstructive or only partially so, is practically never an emer-

gency. The time necessary for careful observation, correct classification and proper preparation of the patient for surgery is well spent. During this period, which in some cases may last up to several weeks, the general condition of the patient can be greatly improved by medical management. This reduces the postoperative morbidity and mortality, not to mention the danger of precipitous unnecessary operations because of incorrect diagnosis of the cause of the jaundice.

In the preoperative management several considerations must be stressed, all of which are more important if the jaundice persisted for more than 4 or 6 weeks, than in the acute cases. Because of back pressure upon the liver in the more chronic cases hepatocellular damage is likely to have occurred and this adds seriously to the operative risk. To minimize the danger of the operation all deficiencies must be combated as far as possible. This means the treatment of dehydration by proper hydration, usually by the intravenous route. Here a word of warning is necessary about the danger of excessive amounts of saline, which predispose to dependent as well as pulmonary edema. Intravenous glucose should be given routinely in the preoperative stage. Amino acids, plasma or human albumin to restore a hypoproteinemia (if present) is likewise given intravenously. The prothombin time must be carefully watched. If a deficiency is found in this respect, Vitamin K must be administered to restore it to normal before an operation. In instances where there is no response to Vitamin K, usually the result of serious liver damage, the prothrombin time can be improved by fresh blood transfusions. Vitamin C should also be given, since its absence interferes with proper healing of wounds and delays the convalescence. If an anemia is present, blood transfusions are indicated. The best immediate results of surgery upon the extrahepatic biliary ducts are obtained if it is done when the icteric index has either reached a plateau or is declining. Therefore, the hyperbilirubinemia must be repeatedly estimated to select the proper time for an operative intervention. Other incidental diseases such as cardiac, respiratory or renal should be treated preoperatively in an approved manner.

The immediate postoperative treatment of these cases is best carried out by an experienced surgeon. Hence, we will not discuss the problem of blood or plasma transfusion on the operating table or soon afterwards, the use of oxygen or the aspiration of the bronchi when indicated. Neither is it within the province of this presentation to elaborate upon the care of the wound, T tube, or early ambulation. We abstain from a discussion about ligation of veins versus heparin or dicumerol in prevention and treatment of thrombophlebitis and pulmonary infarction. But within 3 to 5 days after an operation, dietetic and other considerations make it advisable for a medical man to assume an almost equal responsibility for the care of the patient.

As soon as possible, one should place the convalescent patient on an adequate diet with due consideration for his ability to digest, absorb and assimilate the food. Thus, if a patient has an external biliary fistula and no bile reaches the bowels, fats are neither digested nor absorbed and therefore should be excluded from the diet. The food should be in an easily digestible form and should contain sufficient

calories at the earliest possible time, enough proteins to restore the nitrogen balance and high amounts of carbohydrates for glycogen storage in the liver. If food in sufficient quantity cannot be given orally, supplementary intravenous alimentation becomes a must. Adequate amounts of fluids either by mouth or parenterally should be given. One must at all times bear in mind the danger of excessive hydration particularly in patients with cardiac or renal defects. In the presence of serious liver damage and where a large amount of bile is lost, repeated prothrombin time studies should be done. If a deficiency in this respect is found, parenteral Vitamin K should be administered to control it. When bile is lost through a T tube for a long period or a permanent external bile fistula exists, bile must be given by mouth in the form of a bile cocktail or as bile salts to prevent chemical changes which occur with its prolonged loss. In the postoperative management of jaundiced patients where the pancreas is either destroyed by disease or resected, the oral administration of lipocaic[37] is advisable to prevent fatty infiltration of the liver.

Any incidental preoperative disabilities, such as cardiac, pulmonary, renal, etc. disturbances, should be appropriately treated postoperatively. Likewise, medical complications which might develop postoperatively should be considered and treated accordingly.

Summary

Jaundice often is an important sign of a diseased state which requires active medical or surgical treatment. The treatment of this condition depends upon proper classification. It is discussed under four headings. First, jaundice of undetermined origin; second, prehepatic; third, hepatocellular and fourth, posthepatic.

The treatment of the undetermined and hepatocellular cases is medical and consists of rest and liver management, which is outlined. The treatment of the prehepatic consists of proper care of the underlying disease and does not require liver management. The treatment of posthepatic jaundice is primarily surgical and medical management is limited to pre- and postoperative phases of it.

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SURGICAL THERAPY IN JAUNDICE*

WALTER B. CRANDELL, M.D.†
White River Junction, Vt.

Any discussion of surgical therapy in jaundice resolves itself along two lines of thought: (a) the general surgical problems in the presence of jaundice and (b) the relief or treatment of jaundice by surgical measures.

The jaundiced patient subjected to surgery, particularly major surgery, is vulnerable to certain complications peculiar to that disease and resulting from certain metabolic disturbances. Difficulties may arise while preparing the patient for surgery, during the operation, or in the postoperative period. In the presence of either hepatogenous or obstructive jaundice there is always some impairment of liver function and diminution of bile flow. The seriousness of the metabolic disturbances is quite variable and is related to the cause of the jaundice, the severity of the primary disease, and the length of time it has existed. To grasp the complexity of the situation one must recall that the liver performs a veritable multitude of functions and that there is considerable variability of the extent to which those functions are individually or collectively disturbed. Our concern is chiefly with that group of patients who have obstructive jaundice or who present a picture so closely resembling obstructive jaundice that surgery must be performed. Time does not permit a complete review of the known functions of the liver and the related surgical problems resulting from a disturbance of each. However, certain of those disturbances which at present are thought to be most important should be emphasized and will be discussed briefly.

Manufacture and Secretion of Bile Salts:—The most important constituents of the bile, and specific secretions of the liver, are the bile salts[1]. They are necessary for the absorption from the gastrointestinal tract of (a) fat; (b) fat soluble Vitamins A, D, and K and (c) iron and calcium[2].

Difficulty in fat absorption lowers the caloric intake and if the carbohydrate consumed in the diet is inadequate to compensate, essential proteins may be used as calories, an extravagant body process. Also, fatty livers, wherein liver protein and glycogen are replaced by fat, can be produced by inadequate caloric intake[3] as well as by obstruction to the common duct[4]. Although adequate absorption of Vitamins A and D is important to proper body function, impaired absorption of Vitamin K has produced complications of the gravest nature during surgery on jaundiced patients[5, 6]. Prothrombin, an important factor in blood clotting, is manufactured in the liver from an unknown substance, but the process is dependent on an adequate supply of Vitamin K. Since the absorption of Vitamin K is through

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†Chief of Surgery, Veterans Administration Center, White River Junction, Vermont. Assistant Professor of Clinical Surgery, Dartmouth Medical School, Hanover, New Hampshire.

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combination with desoxycholic acid, a constituent of bile, biliary obstruction prevents absorption, leading to a prothrombin deficiency and undesirable bleeding[7]. Added to this is the inability of a seriously damaged liver to manufacture sufficient prothrombin even in the presence of an adequate supply of Vitamin K. Prothrombin time should be routinely performed, and synthetic Vitamin K given intravenously. A poor response in the event of an abnormal initial figure signifies severe liver damage. Large intravenous doses may be necessary and a normal prothrombin figure should be obtained before surgery is instituted. Stored blood is deficient in prothrombin, so in the patient who does not respond to massive doses of Vitamin K but in whom surgery is imperative, transfusions of fresh whole blood are required.

Protein and Nitrogenous Metabolism:—The role of the liver in protein metabolism is an intimate one, assuming increasing importance with further acquisition of knowledge[8, 9, 10]. In the normal individual there are some 7 grams of protein per 100 cc. of plasma. Since the circulating plasma volume averages 3,500 cc., this means 245 grams of protein are circulating. It is of some importance to bear these figures in mind since, in a patient who is dehydrated or undernourished, the laboratory may report a normal total protein of 7 grams. Following hydration or improved nutrition, restoration of a normal blood volume may permit the true state of protein depletion to be revealed[11]. The plasma volume and proteins are the elusive but effective values with which we are concerned. It must also be recalled that a lowered plasma protein level is a reflection of depletion of tissue proteins, a mass thirty times as great which consumes 30 out of every 31 grams of protein given to restore a lowered plasma protein level[12]. In the presence of appreciable weight loss, lowered serum proteins should be suspected regardless of the laboratory results.

In the animal deprived of protein, the liver is more susceptible to injury by hepatic toxins and is less capable of carrying on its functions than when the protein intake is sufficient[3, 13]. Moreover, the liver protein acts as a reservoir and in brief periods of inadequate protein intake it undergoes a rapid depletion as exemplified by the rat which, during 48 hours of starvation, loses 20 per cent of its liver protein, while the other tissues average 4 per cent loss[11]. That a similar situation may exist in the human is strongly suggested by the work of Cole et al.[15] on 92 patients undergoing simple operations such as herniotomy and cholecystectomy. Practically all patients showed impairment of liver function for two to five days following operation, the cholecystectomy patients more than the herniotomy patients. In cases in which there were complications the impairment of liver function was considerably increased. Except in the presence of complications, the impairment could be prevented by a high protein diet.

Eighty-five per cent of the osmotic pressure of the blood proteins is exerted by the small albumin molecule which composes only 65 per cent by weight of the plasma proteins. It is probable that all the albumin and fibrinogen and some of the globulin fraction is manufactured in the liver[8]. There is often a low albumin fraction in liver disease, disturbing the normal albumin-globulin ratio. It is

important to correct this condition if possible, since the osmotic pressure of the blood is less and the hypoproteinemic patient more readily slips into shock[16]. Also, the lack of the usual hepatic albumin reserve is one of several reasons why the shock is more likely to be serious and less responsive to ordinary corrective measures.

Fibrinogen, the soluble precursor of the insoluble fibrin, is also manufactured in the liver. Severe liver damage or inadequate protein dietary intake contribute to decreased fibrinogen blood levels, and this may cause hemorrhagic tendencies during surgery[17].

In attempting to correct these deficiencies, a good oral intake is the basic route of replacement. It is particularly important to stress an increased intake of total calories as well as protein so that protein will not be burned for energy.

We have found that palatable diets are most successful in producing satisfactory results. Often when we have been too idealistic in our desires for a particular distribution of amino acids or an unpalatable, low fat content, the number of calories and grams of protein consumed by the patient have been unsatisfactory. And it is these factors which have seemed to us to be most important in restoring weight, strength, and normal blood volume. Skim milk powder is the basis of a formula which is coaxed into the patient with every wile and trick we can devise.

Although the oral intake is most important, the parenteral route is of great aid and its use is increased in proportion to the disability of the patient and the urgency of the surgery. Amino acids, blood, and glucose are all usually needed by the jaundiced patient and some parenteral fluid is given daily.

Carbohydrate Metabolism:—The importance of the liver in carbohydrate metabolism has been appreciated for many years, perhaps slightly overemphasized at the expense of protein metabolism. The liver stores glycogen as well as protein, converts proteins and fats into dextrose when necessary, and is of great importance in maintenance of the blood sugar level[18]. Adequate carbohydrate intake is essential in maintaining proper nutrition of liver cells and protecting them in certain of their detoxifying functions[3].

Detoxification:—In a broad sense, the liver has an important responsibility in removing noxious substances from the body and has four methods by which this may be performed[2]:

1) Chemical—by conjugation, oxidation, acetylation and reduction;
2) Excretion (heavy metals);
3) Storage and/or destruction (morphine);
4) Reticuloendothelial cell activity against particulate material.

The chemical method has been the subject of extensive and prolonged study by many workers and for many years it has been realized that conditions interfering with the ability of the liver to carry out these processes lead to difficulties. The integrity of the hepatic cells is dependent on adequate glycogen and protein stores and is impaired by excessive fat deposition. Besides a diminution in their ability to handle noxious substances, the liver cells become more susceptible to

injury in the process[19]. This ability to conjugate is the basis of some of the tests of hepatic function, though of course only a particular function is measured. Nevertheless, the surgeon managing the jaundiced patient must consider these facts in his choice of drugs and in his dietary management.

Authorities differ as to the choice of anesthetic agent in jaundice and the experimental evidence is conflicting. It is probably true that cyclopropane, ether, or a spinal anesthetic are all well tolerated when given in terms of a satisfactory anesthesia. However, liver anoxia may be produced by either an obstructed airway during administration of a volatile agent or a blood pressure drop during spinal anesthesia, the resultant damage being unrelated to any specific effect of the agent on the liver but nonetheless undesirable.

TABLE I

		Hartmann	Schiff	Lipp	Total
Jaundiced - Total		400	575	412	1387
Jaundiced - Hepatogenous		152	374	175	701
Jaundiced - Obstructive,	#	248	201	237	686
Obstructive,	%	62%	35%	57%	49.5%
Types of Obstructive Jaundice:					
Stone -	#	79	35	152	266
	%	31.8%	17%	64%	38.8%
Carcinoma -	#	84	121	78	283
	%	34%	60%	33%	41%
Benign - Obstructions and Strictures -	#	78	45	7	130
	%	31.5%	22.3%	3%	18.9%

Tabulation of data compiled and computed from Hartman[29], Schiff[30], Lipp et al.[31].

There are also certain other points about the liver which should be considered. About three fourths of the blood supply to the liver is from the portal vein and is venous blood returning from abdominal viscera with an oxygen saturation under normal conditions of 70-80 per cent[20]. In studies on shock by Cournand et al.[21] it was shown that the tissues took up a greater amount of oxygen, as shown by an increased arterial-venous oxygen difference. With its many functions the liver undoubtedly has a high oxygen requirement, so that the organ appears quite vulnerable to damage by anoxemia, especially during shock. Also, work by Fine, Seligman, and Frank suggests that there is formed in the liver during shock a substance which, entering the circulation, adds to the severity and persistence of the shock[22].

In the presence of obstruction to the common duct there is pressure on the hepatic cords and some cellular damage. The severity of the damage is variable but is most certainly diminished by the ability of the liver lymph flow to act promptly in a decompressive manner as shown in animal experiments in which the thoracic duct was canalized during obstruction[23]. It is this factor which allows a certain amount of time to be spent in preparing a patient for surgery even in the presence of complete obstruction.

The proper selection of patients amenable to surgical treatment still remains a difficult task. The history, physical examination, and liver function tests are all required to make a correct decision in the individual case. In general, the tests are directed toward determining either impairment of one of the numerous functions of the liver or obstruction to bile flow. However, certain circumstances may obscure this delineation. In the first place there is usually marked impairment of liver function with the development of a "secondary biliary hepatitis". Second, in certain types of hepatitis there is obstruction of the finer intrahepatic bile canaliculi[24, 25].

A recent aid in the differentiation, used extensively by certain clinics, is the histologic examination of liver cells obtained by needle biopsy[26, 27]. As experience with this method increases, it becomes of greater value. Even when all these methods are employed, reasonable doubt may still exist as to the presence of a lesion that could be surgically corrected. In these instances surgical exploration should be carried out as a diagnostic aid.

In my previous experience on the Third Division Surgical Service at Bellevue in New York City and now at While River Junction, patients are managed according to what might be termed the "modern dynamic theory of surgical care". They are carefully prepared for operation and expertly anesthetized by physician anesthetists. Surgery is careful, as atraumatic as possible, and unhurried. Fluid therapy during operation attempts to replace as precisely as possible the amount and type of fluid lost. Silk technic is used throughout. Drains are employed as infrequently as possible and are brought out through stab wounds rather than traversing the usual transverse incisions. Though transverse incisions cause less rectus spasm and pain than other types, some pain relief is required. A most effective way of treating pain without diminishing the cough reflex is intercostal nerve block with procaine. This is used as necessary and varies in frequency with the requirements of each patient. Early ambulation and the immediate rather high parenteral protein intake described by Co Tui are employed[28].

Surgical treatment has been used with success in lesions all along the course of the bile ducts from the intrahepatic canuliculi to the sphincter of Oddi.

A stone in the common duct is the cause of the obstruction in about 35 per cent of the cases of surgical jaundice[29-32] (Table I). The obstruction is usually incomplete and/or intermittent, and may or may not be accompanied by pain. The clinical and laboratory picture can be quite variable. Since this is the group in which surgery produces the most gratifying results and which is often mistaken for medical jaundice, it is the most important to recognize.

It is unfortunate that in about 40 per cent the biliary duct obstruction is produced by neoplasms. About 75 per cent of these are primary in the biliary system, arising from the pancreas, bile ducts, or gallbladder. Most of the remainder are extensions of tumors originating from adjacent viscera. Benign tumors are rare. The obstruction by tumor is usually progressive and constant and the jaundice becomes severe. Pruritus is frequent and often intractable. Since a certain number of these tumors cause obstruction early while they are still quite localized, an aggressive surgical attitude must be maintained in spite of frequent disappointments. Also in this group surgery has a palliative role: (a) in the relief of pruritis by external or internal drainage[33]; and (b) in the relief of pain by cordotomy or splanchnic nerve section.

In about 20 per cent jaundice is due to benign obstructions of the common bile duct. About 50 per cent give a history of a previous cholecystectomy. In these postoperative strictures, the jaundice is progressive and constant, as with neoplasm, though less likely to be so severe. Operative injury to the common duct has been considered the cause, but recent anatomical studies by Shapiro and Robillard[34] suggest that the blood supply of the common duct may be injured, producing a stricture without direct injury of the duct at operation.

Stone, neoplasms, and benign stricture, together are the etiologic factors in 90-95 per cent of the cases of obstructive jaundice. The remaining 5-10 per cent are caused by a miscellaneous group of disorders, the results of inflammations, infestations, and functional disturbances of the biliary tree, including the biliary pancreatic relationship.

The technical factors involved in the surgery of the common duct obstruction by stone, neoplasms, and strictures have been surgical problems of keen interest for many years and remain so today. There are many excellent expositions on the subject by more capable and experienced explorers of the biliary tract than I, and I will not be so presumptuous as to pass judgment on these papers[35-45].

However, difficult surgery can be made much easier by intelligent preoperative preparation, precise diagnosis, and careful, atraumatic, and unhurried surgery performed on a patient who remains in good condition throughout the operation and who in the postoperative period resumes his locomotor, nutritional, and respiratory activities with minimal delay or pain.

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Discussion

Dr. Louis H. Mendelson (Springfield, Ohio):—I want to congratulate the the speakers on well prepared and beautifully presented papers. It has been a pleasure to listen to them.

I am supposed to discuss Dr. Capps' paper on Differential Diagnosis of Jaundice, and in order to do so, effectively, I think one should do it in detail. In Yater's book on "Symptom Diagnosis", there are eighty some subjects associated with jaundice, so you see, with five minutes' time—and I assure you I won't even take that—I can't do that and do it very well. In order to complicate matters more, I thought perhaps you would be interested in hearing of a case we recently had in Springfield City Hospital.

A man had a transurethral resection. He seemed to be getting along very well, but in about a week he suddenly developed jaundice and in a few days he died. Postmortem examination showed that he had a very large embolus in the portal vein. So the subject of differential diagnosis of jaundice, to me, is still quite difficult. As Dr. Capps said, and I think that it is the concensus of opinion, hemolytic jaundice is a very easy subject to diagnose, but the only way we can diagnose hemolytic jaundice, it seems to me, is by looking for it.

As Dr. Jankelson told you, jaundice may be of a mixed type. There is no reason why we can't have a hemolytic jaundice associated with parenchymal or obstructive jaundice. It, therefore, behooves us to look for it.

As you know, the important criteria for the diagnosis of hemolytic jaundice are (1) the indirect van den Bergh; (2) the variable reticulocyte count and (3) variable anemia.

Another thing that impressed me—in fact, the entire paper impressed me—but something very timely in Dr. Capps' paper, is the subject of needle biopsy. It seems to me that any diagnostic procedure which entails a mortality rate of 1 or 2 per cent is not for the average man to do. For the average man, I think, the old conventional way of peritoneoscopy or direct exploratory is by far the safer and will really reveal more in the long run.

I congratulate those who are so skilled that they report many cases of needle biopsy, in many cases I should say without bad results, or very few—for their skill and good fortune.

Another thing in regard to differential diagnosis of jaundice—we seem to be able to classify them into medical, surgical or hemolytic, but, as the old saying goes, "All signs fail in fair weather." Given an individual who has jaundice and

doesn't improve over a reasonable length of time, let us say thirty, forty or forty-five days, I think that individual, as Dr. Crandell says, is entitled to the benefit of the doubt, and an exploratory operation should be performed.

Dr. Alfred B. Clements (New York, N. Y.):—I should like to express my appreciation to this Association for the privilege of discussing Dr. Capps' interesting paper. The differential diagnosis of jaundice is becoming increasingly important. This is true not only in cases where possible surgical intervention may be indicated but also in those patients who can be subjected to medical therapy in accordance with the newer methods now at our disposal. With proper clinical and laboratory evaluation the severity and duration of the disease may be favorably influenced or even a fatal outcome prevented. Dr. Capps' outline of his approach to this problem merits careful consideration.

Too much emphasis cannot be placed on the importance of a careful history. As Dr. Capps has shown in this presentation and in his many articles on the subject, the virus of hepatitis may be transmitted in many ways. All of these should be investigated. The patient should also be questioned thoroughly with reference to the use of possible hepatotoxic agents for medicinal purposes or occupational exposure to such agents.

Undoubtedly a great advance in the differential diagnosis of jaundice has resulted from the increasing use of liver biopsy either as Dr. Capps recommends by the peritoneoscopic approach or as many prefer by needle biopsy. I do not feel that the average investigator considers the peritoneoscopic method as safe as Dr. Capps does. Needle biopsy can be done in the hospital with a minimum of preparation and negligible risk. It should not be done, however, unless the liver is definitely papable below the costal margin. I feel, as others do, that the intercostal approach is too dangerous and may result in severe bleeding. The danger also exists in that this procedure may be taken too lightly and may be employed indiscriminately by relatively inexperienced investigators who might consider it a harmless diagnostic short-cut.

I should like to ask Dr. Capps if he hesitates to carry out a biopsy on a liver in patients who have a low prothrombin level. Many observers feel that the risk of hemorrhage is too great in these cases. However, we know that many cases of jaundice have a lowered level of prothrombin and, if we adhere too rigidly to such a criterion, we will be denied the benefit of liver biopsy in a fair percentage of cases. At the Bronx Hospital we do not hesitate to perform a biopsy on any palpable liver regardless of the level of prothrombin. However, in those cases, where it is especially low, we have made it a practice to inject Vitamin K intravenously just before the test is done.

As for the laboratory tests of hepatic function, I think that Dr. Capps will agree that they still leave much to be desired and are often misleading. They should be employed with due regard for their interpretation in the light of clinical judgment. We have been studying our liver cases by the usual multiple test method. It seems that every laboratory favors a particular test and ours is no exception to

the rule. This test is the determination of the serum albumin-globulin ratio by protein fractionation with methyl alcohol. We have found that this method has given us rather satisfactory correlation in most of our cases as compared with the cephalin-cholesterol flocculation test or the thymol turbidity test.

In conclusion, I wish to call attention to that group of cases in which improvment does not occur with rest and adequate medical therapy. Where the slightest doubt exists as to the underlying pathology the patient should undergo exploratory laparotomy. Every once in a while, a case of so-called subacute hepatitis turns out to be one of obstruction of the common duct caused by a silent stone.

Dr. Harry Shay (Philadelphia, Pa.):—Mr. Chairman, I was glad to see that in Dr. Wirts there is at least one other person left who still uses the 2 milligram bromsulfalein dose, and I think the time and place is appropriate to raise the question of dosage with regard to that test. I know it is almost general practice to use the 5 milligram dose.

For at least two years now we have returned to the 2 milligram dose in our own laboratory, for several reasons. In the first place, I was impressed with the failure of workers with the 5 milligram dose, to agree on what the normal result should be. Then, if one repeats the five milligram dose on the same individual at short intervals, one often sees normal results, or supposedly normal results on one occasion and, on another occasion, results that must be considered abnormal.

These facts prompted us to investigate what might be happening with regard to the 5 milligram dose. We suspected the possibility of an enterohepatic circulation of the dye, and I think we have proven, at least to our own satisfaction, that such a circulation occurs. With the 5 milligram dose the concentration of dye in the intestine may be such as to allow its reabsorption in sufficient amount to add significantly to the amount of dye left in the blood stream at the end of forty-five minutes or one hour. For the above reasons we have limited ourselves to the 2 milligram dose. We are of the opinion that the 5 milligram dose is not a physiological one.

I should like to ask Dr. Capps if he has done any liver biopsies in the group of patients following serum or infectious hepatitis in whom no evidence of liver disease was present except the elevation of serum bilirubin.

I should like to add one word for the use of methionine in both acute and in chronic liver disease, aside from the facts mentioned by Dr. Jankelson—the role of methionine in supplying methyl groups for transport—the recent work of Vars and Doane in relation to protein metabolism and regeneration in the liver, suggests that methionine may also add a factor that favors regeneration.

In a series of experiments in rats in which they depleted their animals for two weeks by supplying no protein to the diet, they then removed approximately 70 per cent of the liver. When they now added various amounts of protein to the diet, they found that liver protein regeneration was always greater, although to a small degree, when methionine was added, no matter what the level of protein fed.

Dr. William J. Snape (Philadelphia, Pa.):—Dr. Wirts's paper has pointed up two significant facts; first, that the value of continued and expanded efforts to correlate the clinical and laboratory findings must be carried on, and, second, that further work along just such lines as these is necessary before we are able to evaluate and elucidate upon the mechanisms of bile secretion as a whole, both in the normal and in the diseased states.

It is true that bromsulfalein is a useful test for the diagnosis of liver damage; however, we must indicate that our understanding of the fundamental principles underlying the test are perhaps too meagre. Is it not likely that the test would yield more information if we knew the exact mechanism involved in the transferring of the brom dye from the blood to the bile stream, and could we, with certain modifications of the present test, gain data indicating the structural and physiological changes which we do not possess with the present technics?

I think we can make the assumption that the physiological unit of dye or pigment excretion is the blood capillary, the Kupffer's cells, the hepatic cells, the bile canaliculi, and perhaps the lymphatics.

If we add to this system of membranes and interphases the possibility that there is more than a single mechanism of transporting dye across the hepatic cells, we have an exceedingly complicated scheme.

Perhaps it is the altering of these membranes that Dr. Wirts has accomplished in his experiments with choleresis, and if suitable choleretics were available, we might be able to locate more specifically where the liver damage occurs both anatomically and physiologically.

We must not, I feel, continue to be either hidebound to the two or five-milligram dose of dye, but must continue to experiment and use newer and different technics to try to find out exactly in what way the liver is damaged.

In using bromsulfalein dye we are not necessarily merely testing a mechanism whereby a foreign substance is excreted by the liver, but we are probably dealing with some mechanism such as Dr. Wirts, Dr. Cantarow and myself showed, which is involved in the transference and riddance of the blood of bilirubin, and certainly something as fundamental as that, deserves considerably more attention than we have given it so far.

Dr. Emanuel M. Rappaport (Jamaica, N. Y.):—I think that Dr. Wirts has provided a real contribution to the study of the excretory phase of liver function. One of the primary problems that faces internists today is the proper evaluation of the residuals of hepatitis, particularly in those individuals with symptoms and yet without any associated laboratory findings.

When Klatskin and I evaluated some 217 of such cases of chronic hepatitis, we found on an average of about 12 per cent who still had symptoms referable to their previous disease, and yet, using very extensive serial laboratory studies, we were unable to find any impairment of liver function.

I think it is in this group in particular that Dr. Wirts' test may be applicable. It is quite obvious to me that due to the associated technical difficulties of the test, it may not find too much use in cases where the other tests are positive.

Dr. Wirts is to be further commended for his judicious conservatisms in describing the utility of the test, because lately there seems to be overemphasis on the specificity and sensitivity of various tests. For instance, we hear that the thymol turbidity will remain positive longer than any other test in the subsiding phase of hepatitis, or that the thymol turbidity test is significant, when positive, of cellular infiltration in the liver.

I feel that if serial tests are done in hundreds of cases, as we were privileged to do in the army, it will be found that no single test remains positive longer than all others, and as a result, multiple serial tests still have to be done.

It is rather important to correlate the test Dr. Wirts describes with liver biopsy in the group of patients with residual symptoms but without positive laboratory findings. Lately we have been receiving reports of normal liver biopsy findings in many such individuals. It would thus be valuable to find whether, in the presence of a positive biliary bromsulfalein excretion test the liver biopsy is normal because if so, it might prove to be another valuable test in determining functional impairment of the liver without associated morphologic change. I do not believe that a normal liver biopsy conclusively rules out abnormal liver function.

I was going to ask Dr. Wirts two questions, one of which Dr. Shay has already answered, that is, why he correlated his test with a 2 mg/kilo dose of bromsulfalein instead of the more standard 5 mg. dose. In my experience with repeated bromsulfalein tests using the larger dose, with intervals of 7 days between tests, I found no irregularity in results due to the purported reabsorption from the intestinal tract.

Secondly, I should like to know whether or not one has to consider the integrity of gallbladder function in the evaluation of this test.

Dr. Robert F. Scholl (New Haven, Conn.):—I should just like to repeat the observation that has been made before that the high quality of the papers that we have heard doesn't leave us a great deal for the discussion.

First, I want sincerely to compliment the authors, Jankelson and Milner on a concise and common sense approach to their subject.

Our experiences generally coincide with those of Jankelson and Milner. Most of the medications and methods have been generally accepted; a few are still controversial. Their classification of jaundice seems less confusing and complicated than others that have been offered. Its appeal is in its simplicity.

What amazes me is that with such a large cellular and accessible organ to investigate, very little has been known regarding liver function until recent years, and there is much more to be discovered.

We have felt that in hypoproteinemia or reversal of albumin globulin ratio, treatment with amino acids or plasma was not much help. We use transfusions of whole blood; also complete elimination of fat from diet is not indicated, but it

should be low. We are not familiar with the insulin treatment of jaundice unless diabetes mellitus is found. Duodenal drainage has been mentioned as a treatment, but only to be discarded, being of diagnostic value only.

According to Steigmann, who recently published a paper in the Journal of the American Medical Association, some unknown underlying factors cause cirrhosis. It is also difficult to evaluate treatment for this disease because of spontaneous remissions and irreversible stages. Methionine, choline, and cystine, by their lipotropic action remove fat from the liver, this being found the precursor of cirrhosis, according to some authorities.

Dr. Peter J. Serafin (New Haven, Conn.):—Surgical therapy of jaundice presupposes that proper differential diagnosis be made based on complete history, thorough physical examination, and corroborated by such laboratory tests as outlined so clearly by Doctor Crandell.

Seventy-five to eighty per cent of liver tissue can be ablated before marked disturbances of the liver can be ascertained by tests. It is important to bear in mind that the normal liver has a great regenerative capacity, therefore there will be significant variations at certain intervals, in the reading of various liver tests.

Since the degree of jaundice may not be commensurable with the severity of the underlying lesion, every suitable test should be utilized for the complete evaluation of the general condition of the patient.

There are several tests to determine the possible tendency to bleed. That of Ivy is probably the best known; it is easy to perform and gives valuable information about the possibility of bleeding.

Determination of the prothrombin level is of limited value, since about 80 per cent of liver parenchyma must be destroyed to affect the prothrombin reading.

Calcium exerts a rather indirect influence on the clotting mechanism by reducing capillary permeability. In the presence of jaundice the use of calcium is beneficial.

Eiss reports that 4,000 operations on jaundiced patients revealed that 16 per cent of fatalities were due to postoperative bleeding.

Recently liver biopsy is being advocated as a more specific measure of diagnosis. With a 5 inch biopsy needle an adequate specimen can be obtained. This procedure has several limitations one of which is possible hemorrhage. But I believe that this can be easily obviated by the insertion of a plug of oxycel or gel foam immersed in thromboplastin and inserted through a special double sheath, biopsy needle. Jaundiced patients, as a rule, are markedly dehydrated and debilitated, because of vomiting, poor appetite and poor absorption of food from the intestinal tract.

In such cases, we favor giving 10 per cent glucose in lactate Ringer solution; the latter being calculated as 25 cc. per kilogram of body weight per day. This is administered in 1,000 cc. of normal saline. The balance of fluid requirement per day is met by administering 10 per cent of glucose in 2,000 cc. of sterile water

and the total amount per day is computed according to Coller and Maddock's formula. This procedure is carried out for the first few days or until dehydration, or acidosis and alkalosis is corrected.

The degree of dehydration is estimated by hematocrit determination including specific gravity of the whole blood and that of plasma.

Since, approximately 60 grams of glucose can be utilized by a patient in one hour, it is obvious that the speed of glucose infusion should be regulated accordingly, not exceeding 60 drops per minute.

About 15 grams of glucose meets the basal requirements hence 45 grams can be stored in the liver for its protection.

One must bear in mind that the high concentration of glycogen does not protect the liver in the presence of high fat; hence these patients are given no fats. On the other hand administration of amino acids is indicated to keep the patient in positive nitrogen balance. This may be fortified with methionine and vitamins such as vipenta given by mouth.

We prefer spinal anesthesia such as pontocaine, 12 to 14 milligrams with 2 cc. of glucose. This is supplemented by curare. Oxygen is administered during the operation. Only emergency operations are undertaken with the hemoglobin at less than 70 per cent, and blood transfusions or plasma are always given during the operative procedure.

Postoperatively, administration of oxygen by the tent method or mask is always beneficial, for it may prevent the appearance of the hepatorenal syndrome. Whether this serious postoperative complication is due to (1) inadvertent severance of the hepatic artery as it runs close and parallel to the cystic duct; (2) whether it is due to overzealous retraction and microscopic rupture of the liver tissue; or (3) whether it is due to sudden release of pressure in the common duct, has not been determined as yet.

Dr. Crandell is to be congratulated on his very logical and practical approach to the problem of surgical therapy in jaundice.

Dr. Richard B. Capps (Chicago, Ill.):—This matter of liver biopsy seems to have raised quite a bit of discussion. I should first like to make my position clear namely that I think in those cases where it is really essential to establish a diagnosis, regardless of whether you feel that the risk is 1 or 2 per cent or less, that you are justified in performing a biopsy. As a matter of fact, we use a good many other procedures which we know have definite risks and think nothing of it. In the case of a patient where it is a question of a laparotomy and an extensive operation, the risk of a preliminary biopsy is certainly justified, and may save the patient from a laparotomy.

Secondly, the mortality rate from needle biopsy is exceedingly variable and that is one of the reasons there is so much dispute about it. Dr. Leon Schiff, of Cincinnati, had done some three hundred and twenty-five, at last count, without a single accident, and there are some other series, either larger or smaller than

that, without any accidents. Certainly if they are done only on patients with enlarged livers and with proper after-care, the mortality rate is very much less, and I would thoroughly agree with the precautions that Dr. Snape mentioned.

In answer to the Dr. Clements' question regarding whether we do biopsies when the prothrombin is low, we do, if it is not below 50 or 60 per cent.

I might mention here that Shapiro, here in New York, has found that the administration of large doses of Vitamin K, 75 mg. intravenously for four or five days, in people with liver damage actually increases the prothrombin time, and he feels that in some cases this dose may be fatal. This, he thinks, is due to overloading the liver and a depression of liver function.

I think that this must be borne in mind, although so far as I know, his work has not been confirmed. Such attempts as we have made have failed to confirm his findings, but for the time-being I think smaller doses of Vitamin K should be employed.

Now, on the other hand, peritoneoscopy gives a good deal of information that a needle biopsy doesn't. You have a chance to examine the spleen, and you have a chance to examine the gallbladder, and you can perhaps determine the presence of varicosities.

There is a new procedure which Royer and Salari, here in New York, have written about within the last year or two, and which Horan, of Detroit, has been using for four or five years; namely, while the peritoneoscope is in place, the direct introduction of a needle through the abdominal wall into the gallbladder, with the injection of radio-opaque material. In this way you can obtain a beautiful picture of the biliary tract, even in individuals who are severely jaundiced, and determine the presence or absence of obstructions and stones. This is an additional reason why I feel that the peritoneoscope is the most satisfactory way to go about this. Of course, you have to have a trained man, and that is the great difficulty. A man who has had experience with only a few hundred cases, is not thoroughly trained.

In regard to Dr. Shay's question about whether we have done liver biopsies where only the van den Bergh was elevated, we have done only a few and in some the biopsies were normal. In some they have not been normal, and I think this raises an important point: Why should we admit that a liver is normal just because the biopsy is normal? I can't agree with that at all. I think that there are other evidences of liver dysfunction besides pathological evidence. It in no way detracts from the importance of the histological picture, but I think we must bear in mind that the pathology of the liver, particularly in cases of low grade inflammation, is not too well understood or delineated as yet. It not infrequently happens, and Watson feels very strongly about this, too, that you find a normal biopsy in an individual who has both clinical and laboratory evidence of liver dysfunction and liver disease. I am not willing to go along with the idea that the histological picture must be abnormal. I don't believe we know enough about it or have sufficiently adequate histological methods as yet.

In closing I want to thank the discussers for their kind remarks and express my appreciation to the Association for this opportunity to address you.

Dr. C. Wilmer Wirts (Philadelphia, Pa.):—I should like to thank the discussers for their comments and attempt to answer the questions that were raised.

We have employed both the two-milligram and five-milligram doses of dye in performing these tests but prefer the two-milligram dose because the normal values for blood clearance are better established, while the concentration curve and quantity of dye excreted in the bile is comparable with both doses.

As to the technic of the biliary bromsulfalein test duodenal intubation is accomplished in the usual manner employed when performing duodenal biliary drainage. Initially, we sought to empty the gallbladder prior to administering the dye intravenously but after running a control series of patients wherein this was done we felt that the results were no different in the two groups. Therefore we no longer consider this a requisite step.

MECHANISM OF MODERN SERUM TESTS IN RELATION TO THEIR CLINICAL SIGNIFICANCE*†

Magnesium Chloride, Serum Colloidal Gold, Cephalin-Cholesterol, Turbidity Tests

RICHARD BAUER, M.D.
New York, N. Y.

For many years it has been known that changes in serum proteins can be found in certain infectious diseases, especially those accompanied by enlargement of the liver and spleen. For instance, in kala-azar, the formol-gel test caused total coagulation of the serum, while normal sera remained liquid. In the same way, dilution of the serum with distilled water 1:2 gave more flocculation than normal. These findings seemed to indicate an increase in the globulins.

Later on, other tests were developed which were directed toward proving an increase in serum globulins and were used mostly for the diagnosis of liver diseases. These tests have a certain diagnostic value, but the mechanism of the tests could not be adequately explained.

To get a deeper insight into the mechanism of such reactions, we tried to find a test where the conditions could be judged more clearly. For this purpose we used the experience of W. Pauli[1]. Pauli found that the heat flocculation of proteins may be prevented by certain organic and inorganic salts. Especially important for human sera is the fact that a solution of serum albumin does not flocculate if heated with equal parts of a saturated solution of magnesium chloride, while, in contrast, serum globulin flocculates. This gave us the idea of using this difference for a serum test. With this test we have found that there must be an increase of globulins in certain diseases, the main group being liver disorders.

Further investigation established that the euglobulin fraction of the serum flocculates more widely.

Our conclusions were as follows (1934 and 1935):

A positive magnesium chloride flocculation indicates either an increase of the total globulins over 40 per cent of the total serum proteins, or a relative increase of the euglobulin. Especially strong flocculation may be caused by increase of both globulins and euglobulins[2].

In 1937 we developed another serum test and called it serum colloidal gold test. The results were similar to the magnesium chloride test. It was based on the following considerations: The original colloidal gold test was used in the testing

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*From the Research Department of the Manhattan General Hospital, New York, N. Y.

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"The products of plasma fractionation employed in this work were developed from blood collected by the American Red Cross, by the Department of Physical Chemistry, Harvard Medical School, Boston, Mass., under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University." (We wish to express our heartiest thanks for this kind assistance.)

of spinal fluid. It was believed that a special luetic antibody causes gold precipitation in the spinal fluid of syphilitics. Presser and Weintraub[5] proved in our clinic that it was not an antibody that causes the positive test but that in the spinal fluid of certain syphilitics there is an increase and abnormal mixture of proteins. A relative and absolute increase in globulins results in the syphilitic gold curve, whereas an increase in albumin produces the meningitis curve. This experience was used for the development of the serum gold test[3].

A short time later (1938), F. Hanger[7] published a new flocculation test. A cephalin cholesterol extract was flocculated by sera taken mainly from patients with liver disease.

The Hanger test was followed by McLagan's Turbidity Test (1944)[11]. In this test sera of liver-diseased patients cause turbidity in a thymol buffer of pH 7.8 (more recently 7.55[12]).

These four tests were developed between 1934 and 1944. In the first half of this decade when the magnesium chloride and colloidal gold tests were originated, we tried mainly to ascertain that the positive result was due to an increase of the total globulins. It was not possible to determine the role of the separate fractions because the salting-out method did not yield sufficiently pure fractions. Only in the magnesium chloride test did we observe that the flocculating power of the euglobulin fraction was especially marked.

Later on (1937) when Tiselius[6] succeeded in obtaining better fractionation by electrophoresis, and later Edwin J. Cohen[13], by the cold method, it became possible to again study the part played by the separate fractions in the serum tests. The fractions were named alpha, beta, gamma and sub-fractions.

Hanger[9] found that the cephalin cholesterol flocculation is caused by gamma globulin. The albumin from normal sera tends to inhibit the flocculation, if added in sufficient concentration, while the albumin from sera of cases with hepatitis shows less inhibition.

According to Hanger[8] the colloidal gold precipitation caused by gamma globulin was significantly inhibited by addition of albumin. The mechanism of the turbidity test too was studied by Hanger[10]. He concluded that the gamma globulin is not an essential factor in the turbidity test while the presence of lipids is necessary in the test. Extraction of the serum lipids makes a positive test negative, while addition of these lipids renders the test positive again.

The mechanism of the magnesium chloride test has not been studied since the new fractionation methods have been established.

Under these circumstances, it is easy to understand that we too became interested in investigating the mechanism of the above-mentioned four tests. At first we tried to find out which protein fraction causes the magnesium chloride flocculation and which one inhibits it.

Secondly we intended to ascertain and extend Hanger's and our own experiences with the colloidal gold test and, finally, we hoped to bring more light into

the fine and complicated mechanism of the cephalin cholesterol and turbidity tests. This was made possible through the kindness of the Department of Physical Chemistry of Harvard University which supplied us with the following protein fractions.

TABLE I

1. Human serum albumin, 98 per cent pure electrophoretically (Fraction V).
2. Gamma globulin, 95 per cent pure electrophoretically (Fraction II).
3. $Beta_1$-metal containing globulin, 75 per cent $Beta_1$-globulin (Fraction IV-7).
4. $Alpha_1$-lipoprotein containing 16 per cent cholesterol and 35 per cent total lipids (Fraction IV-1).
5. $Beta_1$-lipoprotein containing 35 per cent total lipids (Fraction III-0).
6. $Alpha_2$-globulin, lipid free. 80-85 per cent pure electrophoretically, containing serum esterase (Fraction IV-6).

Experimental Methods

In all flocculation tests it is believed that the albumin does not play a decisive role. It does not contribute to the flocculation. On the contrary, it seems to counteract it. To be sure, we first studied the flocculation of pure albumin solutions in all concentrations, which we find in normal sera and various diseases. To be more explicit, the following is offered:

TABLE II

Reaction of the Separate Protein Fractions in the Four Tests

Human Serum Albumin Fraction V	
Albumin 12.5% sol.—2% sol.	
Magnesium chloride test	Negative
Colloidal gold test	Negative
Cephalin cholesterol test	Negative
Turbidity test	Negative
Gamma Globulin Fraction II	
Magnesium chloride 8% gamma flocculation in 6 tubes	+ + + +
Magnesium chloride 0.25% gamma flocculation in 4 tubes	+ +
Magnesium chloride 0.125% gamma flocculation in 3 tubes	+
Cephalin cholesterol test 4% gamma—0.25% gamma	+ + + +
Cephalin cholesterol test 0.125% gamma	+ + +
Colloidal gold test (McLagan modific.) 8% gamma—0.006% gamma	Positive
Thymol turbidity test 8%—1% gamma	Negative
$Beta_1$-Globulin Fraction IV-7	
Magnesium chloride test 12.5%—2% sol.	Negative
Colloidal gold test 6%—0.4%	Negative
Cephalin cholesterol test 8½%—0.25%	+ +
Cephalin cholesterol test 8%—0.5%	+ + + +
Thymol turbidity test 25% sol.—8%	Negative
$Alpha_1$ Lipoprotein Fraction IV-1	
0.5% Solution	
Magnesium chloride test	Negative
Colloidal gold test	Negative
Cephalin cholesterol test	Negative
Turbidity test	Negative
$Beta_1$-Lipoprotein Fraction III-0	
Magnesium chloride 6.7%—2% (Cloudiness)	No flocculation
Colloidal gold test 6.7%—0.4%	Negative
Cephalin cholesterol test 6.7%	Negative
3.35%	+
1.65%—0.2%	+ to + +
Cephalin cholesterol test (4 ml. Barbital Barbiturate Buffer pH 7.8 instead of 4 ml. saline)	Same result
Thymol turbidity test 6.7%	Negative
$Alpha_2$-Globulin Fraction IV-6	
10%—5% Sol.	
	All Reactions Negative

If we substitute pure albumin solution of 6 to 12 per cent for serum, the following tests stay completely negative:

1. Magnesium chloride;
2. Cephalin cholesterol;
3. Colloidal gold;
4. Turbidity test.

We then studied the flocculation of the globulin fractions. Again, these solutions were substituted for the sera in all concentrations which could be expected under normal and pathological conditions, i.e., from .1 per cent to even 8 per cent and more. The gamma globulin solutions promptly reacted positively with the magnesium chloride, colloidal gold and the Hanger test. The limit of the reacting concentrations was about equal for the Hanger and the magnesium chloride tests. It amounted to about .1 per cent. The colloidal gold test was still more sensitive to gamma globulin, i.e., about 10 to 40 times, if we take into consideration that the test is made with a fourth as much serum as in the Hanger test. Contrary to the positive results with these three tests, the gamma globulin solutions remain fully negative in the turbidity test.

The next globulin examined was the subfraction of IV-4, called IV-7, containing about 75 per cent $beta_1$ globulin. The remaining 25 per cent were 15 per cent alpha globulin and 10 per cent albumin. No gamma globulin was present. The results with this fraction were rather interesting. In the magnesium chloride test there was no flocculation at all, even in high concentrations, up to 8 per cent and more. The same was true of the colloidal gold test, where even 6 per cent concentrations gave only a trace of discoloration. In the same way there was no turbidity reached in the thymol test.

In contrast to these findings, this $beta_1$-globulin flocculated in the cephalin-cholesterol mixture, slightly less than the gamma globulin, which means down to a concentration of .1 per cent-.2 per cent.

Then followed the examination of the IV-1 solution, a lipoprotein, with about 35 per cent total lipid. This fraction remained negative in all the mentioned tests.

After that came our experience with Fraction III-0, a 6.7 per cent solution. This contained a $beta_1$ globulin plus 35 per cent lipids. As the solution was rather cloudy, the results were sometimes difficult to read. With the magnesium chloride test there was a trace of flocculation to be observed, but the cloudiness prevented a clear reading. With the Hanger test in concentrations of 6.7 per cent and 3.35 per cent, there were no flocculations. In lower dilutions down to .5 per cent we found flocculation but the results were not constant. Thinking that the pH would have an influence, we repeated the Hanger serum test with barbital barbiturate buffer, pH 7.8, instead of Na Cl, but we obtained identical results. It may be mentioned here that we repeatedly tried the Hanger test using the 7.8 buffer in place of saline, and always obtained identical results.

The colloidal gold test was always negative with this fraction. In the thymol turbidity test, the turbidity was no greater than the equivalent of the original turbidity of the III-0 solution, amounting to approximately 1-2 units.

Of special interest are the following experiments. We made the turbidity tests of III-0, 6.7 per cent and gamma globulin 16 per cent separately. Both were negative at 7.55 per cent as well as at 7.8 pH. Then we mixed both tests. To our surprise thick turbidity now occurred, soon changing into flocculation. After some hours the precipitate gathered at the bottom while the supernatant fluid appeared quite clear. This supernatant fluid gave only a faint cloudiness with sulfosalicylic acid; for control we made the turbidity tests with pure buffer, instead of thymol buffer. There was no reaction at all. This rules out a pH effect.

We performed the same experiment with the other lipid fraction IV-1; while the latter, as mentioned before, remains negative in the thymol test, IV-1 plus gamma in the thymol buffer, is precipitated almost quantitatively. Again there was no reaction with the buffer alone. We then tried the two lipid fractions with our $beta_1$ globulin IV-7. There was no turbidity, nor did any flocculation result.

These experiments proved clearly that the lipid fractions III-0 and IV-1 alone give no turbidity, but that they do react intensively in the thymol buffer medium with gamma globulin. In this intensive reaction, both the globulin and lipids are precipitated nearly quantitatively. To get a better insight into the quantitative relations between the single components we once varied the gamma contents, the other time the III-0 contents. It seems that the presence of sufficient lipid is more essential than that of gamma. The reaction was still strong with 1 per cent gamma and 6.7 per cent lipid, but not as strong with 2 per cent gamma and 1 per cent lipid. But here further titrations seemed necessary, especially since the IV-1 lipoprotein had a concentration of only 0.5 per cent.

It has been supposed and proved that the lipids play a role in the thymol turbidity test, as ether extraction of the serum lipids makes the test negative, and addition of the extracted lipids, restores the positive thymol reaction. Our experiments demonstrate clearly that in the turbidity test there is an interaction of the lipo globulins and the gamma globulin upon each other.

Examination of lipid-free $alpha_2$ globulin fraction IV-6 containing some albumin gave a negative result in all four tests.

While it was easy to demonstrate how the single separated fractions react in all these tests, it is not so easy to say and understand how they behave and react if they are mixed together as in human serum. The important considerations are the following: pure gamma globulin reacts in the magnesium chloride test down to a concentration of .1 per cent. In the normal serum the quantitative proportion of the constituents is about on the average: 7.5 per cent total protein consisting of 5 per cent albumin, 2½ per cent globulin. The globulins are composed of about .5 per cent alpha, 1 per cent beta and 1 per cent gamma globulin. The question arises why a mixture such as the normal human serum, containing 1 per cent gamma globulin,

does not flocculate in the magnesium chloride test, while a pure gamma solution precipitates down to .125 per cent? For the Hanger test, the same question arises concerning not only the gamma content but the IV-7 beta$_1$ globulin as well.

We were confronted with this same question in the same way in the colloidal gold reaction. It was repeatedly supposed that the presence of so much albumin in the serum prevents the gamma flocculation in the gold test. To study these conditions more extensively we made the following investigation.

For this purpose we tried at first to inhibit the magnesium chloride flocculation of gamma globulin. To this end we prepared mixed solutions of albumin/globulin, 6/4-6/.25. The flocculation persisted in all these mixtures. We further tried to prevent the gamma flocculation by addition of IV-7 and later of the lipid fractions III-0 and IV-1, but again the gamma flocculated as before. Why the

TABLE III

THE INTERACTION OF THE LIPOPROTEINS III-0 AND IV-1 AND GAMMA GLOBULIN UPON EACH OTHER IN THYMOL BUFFER pH 7.55 AND pH 7.8

(A)

I. 0.1 Gamma 16.5% + 6 ml. Thymol Buffer	Clear
II. 0.1 III-0 6.7% + 6 ml. Thymol Buffer	Clear
I + II mixed—Turbidity changing into thick flocculation. After 12 hrs. heavy precipitate, clear supernatant fluid shows faint cloudiness with sulfo sal. acid.	
0.1 1% Gamma + 0.1 6.7% III-0 + 12 ml. Thy. Buffer	Strong Precipitate
0.1 2% Gamma + 0.1 1% III-0 + 12 ml. Thy. Buffer	Precipitate marked but not as strong.

(B)

I. 0.1 IV-1 0.5% + 6 ml. Thymol Buffer	No Turbidity
II. 0.1 Gamma 16% + 6 ml. Thymol Buffer	No Turbidity
I + II mixed—Turbidity changing into heavy precipitation. Clear supernatant fluid gives faint turbidity with sulfo sal. acid.	

INTERACTION OF LIPOPROTEIN FRACTIONS III-0 AND IV-1 AND BETA$_1$ GLOBULIN FRACTIONS IV-7 IN THYMOL BUFFER, UPON EACH OTHER.

I. 0.1 ml. III-0 6.7% + 6 ml. Thymol Buffer	Negative
II. 0.1 ml. Beta$_1$ IV-7 25% + 6 ml. Thymol Buffer	Negative
I + II	No Turbidity nor Flocculation
Ia. 0.1 ml. IV-1 0.5% + 6 ml. Thymol Buffer	Negative
IIa. 0.1 ml. IV-7 25% + 6 ml. Thymol Buffer	Negative
Ia. + IIa. mixed	No Turbidity*

normal sera do not give positive results in the magnesium chloride test, in spite of the fact that they contain a sufficient quantity of gamma globulin, still defies explanation.

The inhibiting factors are neither the albumin nor the other globulin fractions, including the lipoproteins.

When we developed the colloidal gold test in 1937, we already assumed that the albumin counteracts the globulin flocculation. After the discovery and separation of gamma globulin, Hanger studied these conditions more exactly with a modified gold test. He found that in solutions of albumin to gamma globulin of about

*Since completion of this paper, a review of the literature revealed a paper by Henry Kunkel and Charles Hoagland[18]. According to the authors, the thymol turbidity test depends upon the presence both of lipids and of abnormal lipid protein complexes migrating in the beta globulin fraction of the serum. The gamma globulin fraction also plays an important role. The authors assume that the albumin fraction has some inhibiting power.

6/1 the gamma flocculation is inhibited. We had the same experience. Albumin/globulin 6/1.6 showed weak reaction. Albumin/globulin 6/1 did not react.

We continued studying the inhibition of the cephalin test. In 1943 Hanger[8] investigated this question. He concluded that the albumin does not inhibit the gamma flocculation. Later in 1945 Hanger[9] made the interesting observation that albumin prepared from normal sera prevented the gamma flocculation but albumin prepared from hepatic sera did not inhibit the flocculation. We tried the inhibition of the cephalin flocculation of gamma and IV-7 globulin with albumin/globulin solutions 6/4 down to 6/.25 as in the magnesium chloride test. In none of these proportions did we obtain any inhibition. The gamma globulin as well as the IV-7 $beta_1$ globulin flocculated as without albumin.

If we consider the quantitative proportions in Hanger's experiments, we see that the albumin, in order to inhibit the flocculation must amount to about 18/1 to the gamma globulin. In a proportion of 12/1 it does not inhibit it. Considering that in normal sera the proportion of albumin to the flocculating factor is not higher than 4-6/1, it seems that the inhibiting power of normal albumin is not adequately established.

While we were not able to demonstrate any preventing power of albumin we succeeded in showing that one of the globulin fractions inhibits the flocculation in Hanger's test. The IV-7 fraction could not be used as it flocculated itself. The III-0 fraction, though not flocculating in higher concentration, in low concentration rather increased flocculation in Hanger's test. We therefore tried the IV-1 lipid fraction representing a lipoprotein of $alpha_1$.

As this solution had a concentration of only .5 per cent we mixed .1 cc. of 2 per cent gamma with .1 cc. of .5 per cent IV-1. The gamma content was further diminished to .1 cc. of 1 per cent, .5 per cent, .25 per cent. The control tests contained only gamma. While the gamma solutions flocculated promptly as always, wherever IV-1 was added, flocculation was prevented. One part of IV-1 inhibited the flocculation of 4 parts of gamma. We wish to mention that the pH of IV-1 was 7.4. As the $beta_1$ globulin IV-7 flocculates too in Hanger's test with about the same intensity as gamma globulin, we mixed IV-1 lipoprotein in the same way with $beta_1$ IV-7 globulin. IV-1 prevents the flocculation of IV-7 as well as of gamma globulin. These experiments prove that IV-1 lipoprotein is a definite inhibiting factor of the cephalin flocculation of gamma and $beta_1$ globulin.

Now we went a step further. If the Hanger test is caused by flocculation of gamma globulin and $beta_1$ globulin IV-7 and IV-1 lipoprotein inhibits both precipitations, it must be possible to prevent the positive reaction of a serum by addition of IV-1. We really succeeded in this effort. We took one + + serum (infectious hepatitis) and a + + + positive one (liver cirrhosis). Now we added to .2 cc. serum .1 and .2 cc. of the .5 per cent IV-1. As controls we added .1 and .2 cc. of .5 per cent albumin. While the controls stayed positive the samples where IV-1 was added became completely negative. These experiments proved clearly that a

TABLE IV

INHIBITION OF GAMMA GLOBULIN FLOCCULATION IN CEPHALIN CHOLESTEROL TEST BY ADDITION OF ALPHA LIPOPROTEIN FRACTION IV-1.

0.1 Gamma 2%	0.1 Gamma 1%	0.1 Gamma 0.5%	0.1 Gamma 0.25%	
4 +	4 +	4 +	3 +	Test
0.1 Gamma 2%	0.1 Gamma 1%	0.1 Gamma 0.5%	0.1 Gamma 0.25%	All four tests
+ 0.1 IV-1 0.5%	+ 0.1 IV-1 0.5%	+ 0.1 IV-1 0.5%	+ 0.1 IV-1 0.5%	Negative

INHIBITION OF BETA$_1$ GLOBULIN FRACTION IV-7 FLOCCULATION IN CEPHALIN CHOLESTEROL TEST BY ADDITION OF IV-1 LIPOPROTEIN.

0.1 IV-7 2%	1%	0.5%	0.25%	
4 +	4 +	4 +	2-3 +	
0.1 IV-7 2%	1%	0.5%	0.25%	All four tests negative
+ 0.1 IV-1 0.5%	0.5%	0.5%	0.5 %	

INHIBITION OF POSITIVE CEPHALIN CHOLESTEROL SERUM FLOCCULATION BY ADDITION OF ALPHA LIPOPROTEIN FRACTION IV-1.

Inf. Hepatitis	Serum 0.2	0.2 + 0.2 0.5% Alb.	Serum 0.2 + 0.2 IV-1 0.5%	Serum 0.2 + 0.1 IV-1 0.5%
	++	++	—	—
Portal Cirrhosis	Serum 0.2	0.2 + 0.2 0.5% Alb.	Serum 0.2 + 0.2 IV-1 0.5%	
	+++	+++	—	

"Hanger positive" serum can be rendered negative by addition of the lipoprotein IV-1.

Concerning the turbidity test we were glad to have found some facts contributing to the understanding of the positive test. The study of any inhibiting action which certainly exists may be withheld until later.

After studying the inhibiting factors of the serum, we approached the problem from another angle. From quantitative determinations we know that the normal contents on gamma globulin in human sera amount to about 1 per cent. When the flocculations become positive as in liver diseases, the gamma content increases double and more. This time we tried to make a negative magnesium chloride and cephalin test, positive. To normal negative sera we added increasing quantities of gamma globulin, i.e., to .9 cc. of normal sera, we added .1 cc. of 4 per cent, 6 per cent-12 per cent of gamma globulin, in this way increasing the gamma content by .4-1.2 per cent. The reactions become positive mostly by an addition of about 1 per cent gamma globulin. There was not much difference in this respect between the two tests.

TABLE V

MAGNESIUM CHLORIDE—CEPHALIN CHOLESTEROL NEGATIVE SERA MADE POSITIVE BY ADDITION OF GAMMA GLOBULIN.

0.9 ml. Negative Serum + 0.1 ml. 6% Gamma Globulin stays negative in Magnesium Chloride and Cephalin Cholesterol tests.
0.9 ml. Negative Serum + 0.1 ml. 8% Gamma Globulin stays negative in Magnesium Chloride and Cephalin Cholesterol tests.
0.9 ml. Negative Serum + 0.1 ml. 10% Gamma Globulin . . . . .
Magnesium Chloride Test + + Cephalin Cholesterol Test + +

DISCUSSION

A survey of the above-described observations leads to the following considerations: we were able to find positive factors of all the four studied tests. We could as well detect the inhibiting action of certain fractions. We could make negative sera positive and positive ones negative, but we must assume that the whole fine mechanism of the tests needs still further study and clarification. Therefore our knowledge of the mechanism of the four tests is still incomplete and conclusions drawn must be expressed with caution and reservation. We feel permitted to summarize our results as follows:

The magnesium chloride test is based upon the increase in gamma globulin. Albumin, as well as the other globulin fractions, does not flocculate nor could any inhibiting function be demonstrated. As former experiences show, the 3 and 4 plus reactions are found with sera which have a relative and absolute increase of globulins.

In the colloidal gold reaction the only reactive factor is the gamma globulin. In normal sera the albumin prevents the flocculation of the gamma globulin. A positive result most likely indicates a relative and absolute increase in gamma globulin.

The cephalin cholesterol test is caused by gamma globulin and a $beta_1$ globulin fraction IV-7, the iron binding sub-fraction of IV-4. We could prove the IV-1

TABLE VI

Disease	Mg Cl_2 Test	Colloid. Gold McLagan Modif.	Cephalin Chol.	Turbidity	Remarks
Typical Infectious hepatitis 3rd week 5th week	3rd week ++++ 4th week ++ 5th week Negative	3rd week +++ 5th week ++	3rd week ++++ 4th week +++ 5th week Negative	3rd week 8 units 5th week 5 units	5th week-7th week Total Protein - 7.7% Albumin 5% Globulin 2.7 8th week Ict. subsiding Slow clinical recovery
Infectious hepatitis 2nd-5th week 2nd-5th week Food poisoning in young man. Course like catarrhal jaundice.	Negative Negative		Negative Negative + + — Negative	1-2 neg. Units Neg. Neg.	Ict. Index 65-56 3rd week oral Galactose - 4.6 gr. End of 5th week recovery sets in. After disappearance of ict. Normal visualization of gallbladder. (X-rays)
Acute Atrophy of Liver	++++	Negative	++++	3 units	Autopsy
Chronic passive Congestion of liver due to heart failure. Ascites, Edema Spleen-tumor (Heart Cirrhosis)	++++	Negative	Negative	1 unit	Total serum protein 7.5% Globulin 4.25 Albumin 3.25 Chronic digitalis treatment
Portal cirrhosis Ascites, Edema	++++	++++	++++	7.5 units pH 7.55-7.8	Total serum Protein 8.5% Globulin 5.0% Albumin 3.5% Autopsy
Ca of Gallbladder (Metastases in liver diffuse, small)	Negative		Negative	1 unit	Biopsy

This table could be widely enlarged only showing that in any group of liver diseases all tests are rarely equally positive. It may be stressed that in advanced cases of liver metastases and malign obstruction of the larger bile ducts one or more of the tests may prove strongly positive. (Bauer[4] 1945).

lipoprotein as inhibiting factor for both globulins, while the inhibiting action of albumin was not clearly ascertained. We were able to make a positive serum negative by addition of IV-1 lipoprotein.

In the turbidity test, the gamma globulin played a decisive role on one side and the lipoproteins III-0 and IV-1 on the other. None of these fractions reacts positively with the thymol buffer, but if one of the lipoproteins gets mixed with gamma, both are quantitatively precipitated in the thymol buffer. Thus the turbidity test is caused by interaction of gamma globulin and lipoproteins upon each other in the thymol buffer.

Clinical Application

These facts illustrate that the four mentioned tests have a mechanism similar in some aspects but not at all identical. Each test reacts according to its mechanism and not more. Every attempt to make the individual test more sensitive—to refine it—is not promising and may only lead into error. Though the four mentioned tests are known to be positive within certain groups of liver diseases, we cannot expect that in each individual case the reactions may always be equally positive. Out of a multitude of cases, some examples may illustrate this situation.

A glance at Table VI may give rise to thought. It is certainly necessary and justifiable to use these tests for differential diagnosis. On the other hand, it has been demonstrated that each test, according to its mechanism, is indicative of certain changes which have occurred in the constitution of the serum and of certain quantitative and perhaps qualitative alterations of the serum components. If that is true, it appears logical to employ the results of these tests besides using them for differential diagnosis, for the classification of the different groups of liver diseases and especially for the interpretation of the individual case. It is certainly remarkable that the case of heart cirrhosis reacts positively only with the magnesium chloride test, while the three other tests are fully negative. It is further noteworthy that the one case of socalled catarrhal jaundice stays negative with three serum tests. It is generally assumed that such cases are due more to cholangiolitis than liver cell injury, but the positive galactose test contradicts such an explanation in this case. It is also interesting that the case of liver atrophy is highly positive with the magnesium chloride and Hanger tests, while rather negative in the colloidal gold and turbidity tests.

Our investigations give us some hint that these findings rely upon certain different modifications in the serum components. For instance, a sole 4 plus magnesium chloride test in the case of heart cirrhosis indicates a special relative and absolute increase in gamma globulin, which is supported by the findings of high total protein content and an especially low albumin/globulin quotient.

In infectious hepatitis the magnesium chloride test is strongly positive mostly in the beginning and relatively soon becomes weaker and negative. This seems to indicate that the gamma globulin increase soon subsides. It is made probable by the normal albumin/globulin ratio found in the latter course of this disease. In the cited case of liver cirrhosis, all four tests are 4 plus positive. This suggests a

change in gamma IV-7_1 and both lipoproteins IV-1 and III-0. We have seen that the Hanger test may be due to an increase in gamma or IV-7 beta$_1$ globulin, but is inhibited by the lipoprotein IV-1. The turbidity test is connected with the change or increase of both lipoproteins and their interaction upon the gamma globulins but not the IV-7 beta$_1$. Consequently, if the Hanger test is negative but the turbidity test strongly positive, it is likely that the increased quantity of IV-1 inhibits the Hanger test but favors the turbidity test. If the cephalin test is positive but the turbidity test negative, it is probable that the IV-7 beta$_1$ globulin may be especially increased to which the lipoproteins have no affinity.

As we have demonstrated that each test, according to its nature, is indicative of certain changes in the serum constitution, it seems desirable to have as many tests as possible. But we do not need new tests for differential diagnosis, because no single test will ever suffice for this purpose. What we need are tests based on as many different mechanisms as possible. By means of such tests, we could gain new insight into the changes of the serum components, and use them for interpretation of groups and individual cases.

Summary

The mechanisms of four serum tests have been studied.

The human sera contain positive components effecting flocculation or turbidity, and inhibiting substances.

In the normal serum, a balance between these two factors keeps the test negative.

Under pathological conditions this balance is disturbed.

In the magnesium chloride test, the gamma globulin is the flocculating factor. Addition of gamma globulin makes a normal serum positive.

In the colloidal gold test the gamma globulin is the active factor, while albumin inhibits.

In the cephalin cholesterol test, the flocculation is caused by gamma and beta$_1$ IV-7 globulin. The lipoprotein IV-1 prevents both flocculations. Addition of gamma globulin makes a negative test positive.

On the other hand, addition of IV-1 makes a positive serum negative.

In the turbidity test none of the individual fractions causes any turbidity, but mixture of the lipoproteins on the one side with gamma on the other side results in total precipitation of gamma plus lipoproteins. The lipoproteins do not react with IV-7 globulin in the thymol buffer. Thus we can demonstrate that the turbidity test relies upon interaction of the lipoproteins and the gamma globulin upon each other in the thymol-buffer medium.

Each of the serum reactions mentioned here is based upon a certain complex mechanism. Not all factors of the mechanisms are known but the role of some of them has been demonstrated. Under pathological conditions, as in liver diseases, one or the other, or even all four reactions may become positive, each positive result indicating a certain, not identical change in the serum constitution. But even

in severe liver diseases not all four reactions are always positive or they may change in intensity, appear and disappear in the course of the disease.

By considering these different results of the tests and by evaluating the serum tests with regard to their mechanism, we are enabled to describe the changes in the serum composition that have occurred in the special case. This allows an additional interpretation of the single case and may open new prospects in diagnosis, prognosis and therapy.

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STERCORAL ULCERS OF THE TERMINAL ILEUM

ALOIS POLLAK, M.D., F.A.C.S.*
Los Angeles, Calif.

Few cases of stercoral ulcers of the intestinal tract have been reported. Some writers have reported stercoral ulcers of the large intestine but none of the small intestine, although stercoral ulceration in the intestinal tract due to stasis of the fecal stream, plus increased intraluminal pressure, is not rare. According to Bockus[1], ulcerations are occasionally found proximal to an obstructing lesion in regional ileitis. O'Reilly[6] in the British Medical Journal has reported a death following perforation of a stercoral ulcer of the transverse colon. In his case a large ulcer (about 4 inches long) was found lying in the long axis of the transverse colon, with three small perforations in the bowel wall. The large intestine proximal to it was enormously dilated and filled with fecal masses from the cecum to the transverse colon. There was no histological report of this case.

Sperling[7] reports a case of perforation of the transverse colon distal to a cecostomy which had been performed 12 days before for intestinal obstruction due to a constricting carcinoma of the rectum. Autopsy showed edema of the wall of the lower portion of the ileum near the ileocecal valve. There was no obstruction of the small bowel. The entire colon was moderately dilated as far as the sigmoid flexure. Three perforations, each approximately 4 cm. in diameter, were evident in the colon, one in the transverse colon, one in the splenic flexure and one in the sigmoid flexure at the brim of the pelvis. The edges were black and appeared necrotic. The peritoneal cavity was filled with feces and showed signs of fecal peritonitis. The mucosa of the cecum and ascending colon was reddened and edematous. Beginning at the hepatic flexure, irregular patches of ulceration involved the mucosa and submucosa. At the splenic flexure and in the descending colon these patches fused into an almost continuous, extremely irregular area of ulceration. About 30 cm. above the anus a small adenocarcinoma had completely occluded the bowel. The final diagnosis was carcinoma of the sigmoid flexure with intestinal obstruction and secondary ulceration and perforation of the intestinal wall with fatal peritonitis. The question of the etiology of the perforation and ulceration is probably explained on the basis of fecal impaction, stercoral ulcers, and damage to the circulation of the wall of the bowel by increased intra-enteric pressure.

Boyd[2] discusses stercoral ulcers as follows: "The socalled stercoral ulcer of the mucous membrane develops in the segment above the obstruction owing to the irritation of the hard scybalous masses which collect there. A certain amount of catarrhal inflammation develops in consequence, with the result that there may be periodic attacks of diarrhea, with the passage of semi-fluid matter mixed with mucus.

In cases where fecaliths develop and cause intestinal obstruction, the additional factor of increased intraluminal pressure in the proximal loop will aid as a causa-

*Surgical Staff Cedars of Lebanon Hospital, Surgical Staff French Hospital, Instructor, Department of Surgery, College of Medical Evangelists.

tive factor in this type of ulcer. The histological changes of the bowel wall subjected to obstruction have been thoroughly investigated by Carlson and Wangensteen[3] and by Sperling[8]. Gatch and Culbertson[5] and Dragstedt, et al.[4] measured the rate of the circulation through the intestinal wall during increased intraluminal pressure. They all found that if the intraluminal pressure is increased, the blood flow decreases, but they were unable to shut off completely the mesenteric circulation by increasing the intraluminal pressure.

Sperling found quite pronounced changes in the bowel wall depending on the degree of intraluminal pressure, the changes ranging from petechial hemorrhages of the intestinal wall to necrotic areas with an abnormal amount of permeability.

Fig. 1—Carcinoid of Terminal Ileum.

The case presented here shows the effects of stasis of the fecal stream, with the formation of stercoral ulcers in the intestinal wall proximal to the chronic incomplete obstruction (Fig. 1).

Case History:—The patient, a 58-year-old white male, was seen in my office complaining of lower abdominal pain which he traced back over a period of five years. Several times during this period he had been confined to bed from three to ten days with what was variously called "indigestion" or "intestinal flu". He had had occasional attacks of severe pain in the abdominal region associated with vomiting, followed by a period of complete relief for five or six months. He had suffered from constipation for five or six years but had never noticed any blood or mucus in his stools. During the previous two years the attacks had been more frequent. The

pain would start in the left paraumbilical region and radiate to the back. In October 1944 he sought the help of a general practitioner and a complete x-ray study of the gastrointestinal tract at that time did not reveal any pathology. The stool and blood were negative for dysentery. However, the discomfort continued and on February 5, 1945 he was forced to give up his work, as for the past two months slight distention had developed and the pain had been much more pronounced, at times being almost unbearable. The patient was referred to my office. He complained of severe generalized abdominal pain with nausea. There was no vomiting of blood, no urinary complaints, no blood nor mucus in the stools. Previous history: Appendectomy 1915, left hernioplasty 1923, right hernioplasty 1938, operation for recurrent hernia left side 1939.

Fig. 2—Stercoral Ulcers of Ileum.

Examination revealed a tall, thin male. The skin was pale, the tongue dry, with a white coating. The patient was vomiting clear fluid and was apparently in great pain. His blood-pressure was 105/70; pulse 130, regular but not full. The heart on percussion was normal in size, the tones clear. Lungs: expansion equal, no dullness, no rales. Nervous system: pupils reacted promptly to light and convergence. Peripheral nerves: no pathology. Urine: concentrated, trace of albumin, no sugar. Blood: Hgb. 82 per cent; Eryth. 4,660,000; Leuc. 11,300; Neut. 55 per cent; Eos. 1.5 per cent; Basos. 0.5 per cent; Lymphs. 35.5 per cent; Monos. 7.5 per cent; Stained smear normal; Rh factor negative; Group II.

Local Findings:—The abdomen was distended over the thoracic level. There were left and right inguinal scars from hernioplasties and a right lower appendectomy scar. There was no shifting dullness but persistent increased peristalsis,

palpable, audible and visible, in the middle part of the abdomen. No masses could be palpated.

Impression:—Obstruction in lower part of intestinal tract. Immediate surgery was suggested and the patient submitted more than willingly.

Operation:—At surgery a hard mass was found about 15 cm. proximal to the ileocecal junction in the wall of the terminal ileum. The mesentery of the terminal ileum was edematous. Several large lymph nodes were found. Distal to the obstructing mass the bowel appeared normal but proximally several small hard areas could be felt in the bowel wall. No other distinct masses were palpable, nor para-aortic glands. A segment of the terminal ileum 75 cm. long was resected (Fig. 2), including the obstructing tumor and the involved areas proximal to the tumor, with a wedge of mesentery containing the glands. Side to side anastomosis was made with the usual technic in silk. The anastomosis was attached to the abdominal wall with two silk sutures to protect the anterior suture line and the posterior suture line was protected by free transplant of omentum.

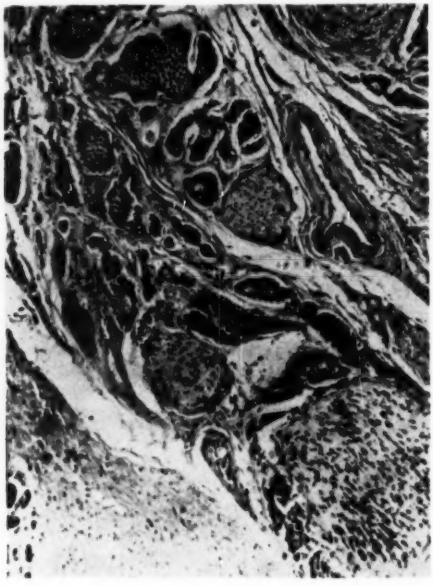

Fig. 3—Microscopic Appearance of Carcinoid.

The patient's postoperative condition was good and he made an uneventful recovery.

Pathological Report:—The serosal surface is dusky red and smooth for the most part but in places is dull and appears to be covered with a thin layer of fibrin. The bowel wall is thickened and edematous in appearance. There is an annular

constriction 4.5 cm. from the distal end which almost completely obstructs the bowel for a distance of 1.5 cm. In this area of bowel constriction the wall of the ileum is thickened, fibrous, and measures 1 cm. The mucosal surface proximal to the tumor shows numerous scattered areas of irregular ulceration varying in size between 0.5 cm. and 5 cm. in maximum diameter. All of the ulcers are shallow and have dark reddish-grey necrotic bases. The attached portion of mesentery is thickened, edematous and shows marked diffuse fibrosis adjacent to the constricted portion of bowel. In the mesentery there are numerous moderately-enlarged lymph nodes.

Microscopic examination of a large representative section taken through the portion of ileum showing the annular constriction shows, infiltrating the wall of

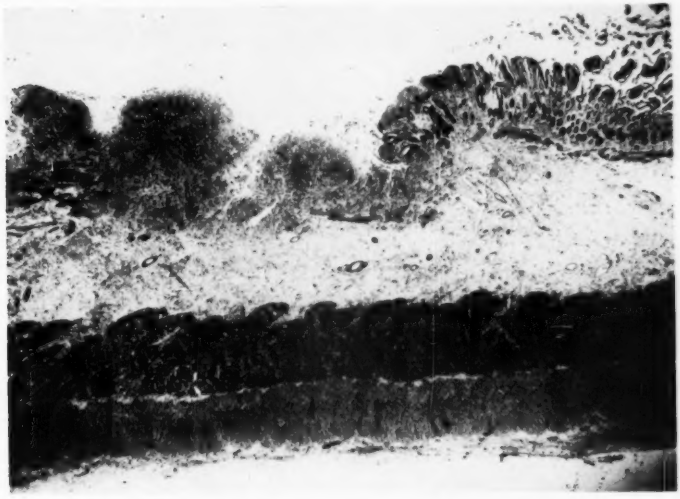

Fig. 4—Microscopic Appearance of Stercoral Ulcer.

the ileum and extending into the adjacent attached portion of mesentery, an abundant growth of tumor cells separated by dense fibrous stroma. The tumor cells are of carcinoid type and occur in solid groups and small irregular infiltrative clusters. There is no glandular arrangement. The tumor cells have uniform, small, predominantly round, deeply-staining nuclei, showing an appreciable degree of pleomorphism (Fig. 3). The mucosal surface is ulcerated but is partly covered with essentially normal mucosal epithelium.

A section taken through one of the ulcers found above the area of annular constriction, noted grossly, shows in the ulcer base a thick layer of inflammatory cellular elements consisting chiefly of lymphocytes, plasma cells, other mononuclear cells and eosinophiles. In the submucosa there is also abundant inflammatory cellular infiltrate and much fibroblastic proliferations. A similar but less extensive inflammatory reaction is noted in the serosa and muscularis. No evidence of car-

cinoid tumor is found in this ulcerated area. Sections of four of the enlarged mesenteric lymph nodes noted grossly show the histologic appearance of hyperplastic lymphadenitis. There is no evidence of tumor.

Diagnosis:—(1) Intestinal obstruction due to carcinoid tumor of ileum.
(2) Multiple areas of ulceration in proximal portion of ileum.
(3) Hyperplastic lymphadenitis of mesenteric lymph nodes.

The histological appearance of the above-described ulcers does not show the signs of chronic distention (Fig. 4). The shallow character of the ulcerations with almost no changes in the muscularis leads to the conclusion that we are dealing with true stercoral ulcers in the lower ileum, a condition which has not been reported before.

The patient has made a complete recovery. Three years after surgery he states that he has gained 50 pounds in weight, is doing an extremely hard day's work every day, has no pain, and has never needed a laxative since his operation.

Summary:—The problem of stercoral ulcers of the intestines has been reviewed and a case presented of a patient with stercoral ulcers in the terminal ileum due to fecal stasis, caused by a slowly obstructing argentaffinoma.

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GASTRIC NEUROFIBROMA*†

(Case Report)

DONOVAN C. BROWNE, M.D.
GORDON McHARDY, M.D.
and
SIDNEY G. MACK, M.D.
New Orleans, La.

Approximately 1.3 per cent of all gastric tumors are benign[1]. Minnes and Geschickter's[2] exhaustive survey of the literature revealed 931 benign gastric tumors; therein were 102 reports of benign neurofibroma of the stomach, an incidence of 10.9 per cent of all benign gastric neoplasms.

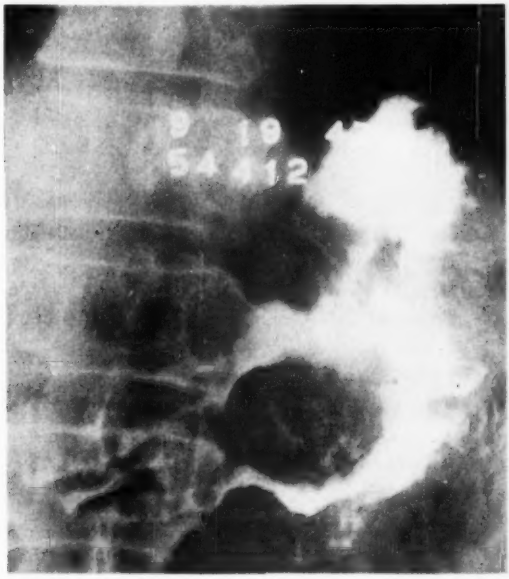

Fig. 1

The site of origin of gastric neurofibroma is not agreed upon. Gray[3], Bailey and Herman[4] believe the tumors to be mesodermal, arising from the perineurium or endoneurium; Masson[5] and Geschickter[6] consider them proliferative lesions of the nerve sheath or ectodermal.

Gastric neurofibromas are more frequent on the lesser curvature of the pyloric portion. They extend either subserosally or project into the lumen of the stomach.

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*From the Gastrointestinal Clinic, Touro Infirmary, New Orleans, Louisiana.

†Especially submitted for publication during the 15th Anniversary Year of the National Gastroenterological Association and the 15th Year of publication of The Review of Gastroenterology, 1948-1949.

Submucosally, they are gray in color with pink or yellow cast, and they are almost translucent with a smooth overlying mucous membrane. Malignant degeneration, reported at thirteen per cent[10], is anticipated more frequently in generalized neurofibromatosis[7]. Although they are rarely symptomatic, their size, location and coexistent ulceration may result in a variety of related symptoms. Ball-valve obstruction would be a textbook characteristic. Concomitant with a benign gastric tumor, peripheral neurofibromatosis would be a classical and almost conclusive diagnostic aid. A familial hereditary history, low mentality and arthritis deformans have been hypothesized[8].

Moore[9] gives the following roentgenological diagnostic criteria for benign gastric neoplasm: 1. The filling defect is circumscribed and punched-out. 2. The defect is usually on the wall leaving the curvature regular and pliant. 3. The rugae are obliterated in the immediate tumor area as in inflammatory and malignant lesions but are more nearly normal. 4. Peristaltic disturbance is minimal and retention is seldom found except when the lesion is pyloric or prepyloric. 5. Niche incisuria or other evidence of spasm are absent. 6. They are rarely palpable.

Benign characteristics permit conservative gastric polypectomy. It is therefore important that all studies including the limited additional value of gastroscopy be applied.

Case C.R.L. (Z11662):—A 52 year old artisan was admitted to Touro Infirmary on September 17, 1947, complaining of localized epigastric fullness of three months' duration. There was postprandial relief; alkali were not ameliorative. Additional pertinent symptomatology included low-grade persistent fever of two months' duration and weight loss of eight pounds. The family history was not significant.

Pertinent to the physical examination were generalized lymphadenopathy, peripheral neurofibromata (histologically benign) and pyrexia (100.4°).

A mild microcytic hypochromic anemia, mild leucocytosis with 15 per cent eosinophilia, and a sedimentation rate (Westergren) of 108 mm. per hour were the only positive laboratory findings.

A roentgen demonstrable polypoid filling defect in the proximal antrum on the lesser curvature was attributed to primary neoplasm, probably carcinoma. Gastroscopy revealed a pedunculated polyp, covered by normal mucus membrane, free of ulceration, gray in color, and producing no peristaltic disturbance and minimal rugal laceration. Gastroscopically, the lesion was considered benign.

On September 26, 1947, after recognizing the benign nature of the polypoid mass, a polypectomy, through a gastrostomy, was done by Doctor James Rives.

Pathologically, the spherical grayish-yellow tumor was a benign neurofibroma showing prominent eosinophilic response.

The patient has remained afebrile and asymptomatic; the lymphadenopathy and eosinophilia have subsided.

Comment:—A rather typical instance of a benign gastric neurofibroma concomitant to generalized subcutaneous neurofibromatosis is presented. The febrile

lymphatic and eosinophilic response are unusual concomitants, considered more than coincidental, but not explained in the literature nor in our single observation.

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EDITORIAL

Cancer Cures

The past decade has seen many unsuccessful attempts at the discovery of a reliable curative agent of malignant neoplastic disease. The latest attempt was made by a group at the University of Moscow.

Roskin and his associates[3] have reported the effect of infection with Trypanosoma cruzi, the causative agent of Chagas' disease upon cancer. In experimental animals already affected with cancer, injected trypanosomes are absent from the organs in which they are customarily found in noncancerous animals—heart, spleen, liver, bone marrow and lymph nodes—and are found only in the neoplasm where they destroy the malignant growth presumably by the elaboration of some specific cancerolytic substance. The group has been able to culture the trypanosomes and to isolate the specific agent from the cultivations.

The group used the trypanosome extract therapeutically in 18 patients with cancer of the breast, larynx, uterus and lips. Final destruction of the tumor with definite preliminary evidences of this (softening and shrinkage) within a week after daily injections of the preparation were begun, were noted in eleven cases. Recurrences were not noted in any of the successful cases.

American investigators have failed to confirm the Russian underlying experimental work. At the California Institute of Technology, Cohen et al.[1] followed the Russian technic, but carcinolytic effects were not noted microscopically. Specific carcinolysis, however, were demonstrated in parallel tests with culture filtrates of Sporosarcina ureae and Aspergillus fumigatus.

Other work is now reported by Hauschka and Goodwin[2] of the Institute for Cancer Research, Philadelphia. All of the strains of Trypanosoma cruzi used by the Russian investigators were tested against spontaneous and transplanted malignant tumors in over 1,000 experimental mice. With the more virulent strains, there was inhibition of the neoplastic growth, but there was no lengthening of subsequent life in the cancerous mice beyond that of untreated controls. In contradistinction to the results of the Russian investigators, this group found no positive cancerolytic effect; they found the usual distribution of the trypanosomes which occurs in normal mice; and this appears to deny any elective localization in the neoplastic tissue which the Russians claim. The Americans conclude that any such unusual distribution is a nutritional effect; this is borne out by the fact that controlling the infection with quinoline restores the "normal" rate of growth of the cancer to an eventual fatal end. The use of tissue filtrates were not effective in cancerous mice, did not prolong life, and death among the treated mice frequently occurred sooner than in the untreated controls.

It is regrettable that the work of the American investigators does not corroborate the work of the Russian group.

A. O. Wilensky

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NEWS NOTES

National Gastroenterological Association Lecture

The National Gastroenterological Association Lecture given by Hahnemann Medical College was delivered at the College in Philadelphia, Pa. on Thursday, 27 January 1949.

The speaker was Dr. I. Snapper of Mt. Sinai Hospital, New York who spoke on "The Treatment of Uremia in Hepatic Insufficiency".

This National Gastroenterological Association Lecture is the first of a series of Annual Lectures to be sponsored by Hahnemann Medical College of Philadelphia and is under the supervision of Dr. Harry M. Eberhard, 2nd Vice-President of the National Gastroenterological Association.

Doctors Crile and Wangensteen Accept Invitations to Speak

Dr. William R. Morrison, President and Chairman of the National Gastroenterological Association Program Committee announces the acceptance of invitations by Dr. George W. Crile, Jr., Cleveland, Ohio and Dr. Owen Harding Wangensteen, Minneapolis, Minnesota to speak at the Convention in Boston in October 1949.

From all indications the Boston meeting promises to be one of the most interesting and instructive scientific sessions which the National Gastroenterological Association has yet presented.

The complete program will appear in a coming issue of The Review of Gastroenterology.

In Memoriam

We record with profound sorrow the passing of Dr. R. Molinery of Luchon, France, Honorary Fellow of the National Gastroenterological Association.

We extend to the family of the deceased our deepest sympathies.

Correction

In the Book Reviews, on page 98 of the January 1949 issue of The Review of Gastroenterology the price of "Virus Diseases of Man" by C. E. Van Rooyen, M.D. and A. J. Rhodes, M.D., published by Thomas Nelson & Sons, New York was incorrectly listed as $20.00.

This was the prepublication price and the present cost of this volume is *$22.50.*

To the Editor:

In the December, 1948 issue of The Review of Gastroenterology, in an article entitled, "The Effect of the Antitoxic Principle Upon Hepatobiliary Diseases", Dr. Juan Nasio makes the following statement in discussing prothrombin time: "Divide the coagulation time of the normal subject (dividend) by the coagulation time of the patient (divisor), and the result multiplied by a hundred expresses in per cent the prothrombin concentration as customarily expressed in the North American school". I do not believe that we of the North American school thinks this is so.

Amigen Solution for parenteral administration

Protolysate for oral administration

In the dietetic management of GASTRIC and DUODENAL ULCER there is increasing clinical evidence that

PROTOLYSATE

used orally or by tube, as the sole nitrogenous nutrient or in connection with a bland diet of the Sippy type, BUFFERS GASTRIC ACIDITY, SUPPLIES NITROGEN IN READILY UTILIZABLE FORM with no digestive burden, and aids in rapid healing of the ulcer.

Samples and literature on request.

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P. S. While Protolysate is a hydrolyzed protein, PROTENUM is an intact (high) protein food of low fat content, unusually palatable. Useful in formulating high protein diets and in correcting protein-deficient diets. Suitable for persons of all ages. (One ounce supplies 12 Gm. protein with only 105 calories.) Made by M. J. & Co. For sale in 1 pound tins at drug stores.

Dr. Armand Quick has shown that plasma maybe diluted from 100 per cent down to 5 per cent, and the prothrombin time determined on these varying solutions. Then he has plotted the prothrombin time in seconds against the diluted specimens of plasma, expressing these later values as prothrombin activity in per cent. The resulting curve has been a hyperbole. This has definitely proven that the relationship between prothrombin time and prothrombin activity is *not* a linear relationship. Therefore, dividing the prothrombin time of the normal by that of the patient will not give us a true expression of prothrombin activity.

Within the past year, Dr. Quick has issued a formula which he claims will give us prothrombin activity in per cent if the patient's prothrombin time is known. The formula is:

$$\text{Prothrombin Activity in per cent} = \frac{302}{\text{P.T.} - 8.7}$$

(P.T.—Patient's prothrombin time in seconds)

This formula may be taken for what it is worth. Today most clinics have found it more efficacious to express prothrombin time in seconds, but always to compare it with a normal control.

This is a very prominent issue today, especially since dicumarol therapy has taken such a forward stride in the treatment of coronary thrombosis.

Baltimore, Md. Samuel P. Scalia, M.D.

Dr. Nasio's paper was written early in 1947 and was submitted as an entry in the 1948 National Gastroenterological Association's Prize Award Contest.

Editor

ABSTRACTS

Gastrointestinal Tract

OBSTRUCTIONS OF THE ALIMENTARY TRACT William E. Evans. Radiology. **51**:23, (July), 1948.

The distribution of the more common obstructing or potentially obstructing lesions observed in 400 infants during the past seven years at Children's Hospital of Michigan is the following: Hypertrophic stenosis of the pylorus, 50 per cent; intussusception, 20 per cent; atresias of the esophagus, 4 per cent; atresias of the duodenum, 2 per cent; atresias of the jejunum-ileum, 3 per cent; atresias of the colon-rectum, 2 per cent; atresias of the anus, 5 per cent. Strangulated hernia, 8 per cent; meconium ileus, 2 per cent; congenital bands, 2 per cent; volvulus, 2 per cent.

The age of the patient is often an important consideration in pediatric diagnosis, and this is particularly so in alimentary tract lesions. The atresias, meconium ileus, and most of the cases of volvulus are seen during the first days of life. Hypertrophic pyloric stenosis usually occurs between three and ten weeks of age. It will be noted that there is little overlapping of these three groups. Meconium ileus is difficult to differentiate from ileal atresia, however, if there is no abrupt termination of the gas distended bowel, and if there is a mottled appearance of the meconium and a very small calibre of the colon, meconium ileus may be recognized. Good illustrations show the different pathological conditions.

Franz J. Lust

Stomach

VAGOTOMY IN THE TREATMENT OF PEPTIC ULCER. C. F. W. Illingworth and A. W. Kay. Edinburgh M. J. **54**:540-544, 1947.

The two main objectives of therapy for peptic ulcer—are to reduce gastric acidity and to put the ulcerated area at rest.

In six cases of peptic ulcer treated by vagotomy by the abdominal route the immediate effect was the relief from all symptoms. Recurrence is attributed to regeneration of the cut nerves. Pain recurred in 1 case within 3 months, in 2 cases after 18 months, and a 4th after 27 months.

Vagotomy had a pronounced effect in reducing the gastric motility. It had no effect on the acid concentration of the gastric juice.

Hyman I. Goldstein

ROENTGEN EXAMINATION OF THE STOMACH IN SYMPTOMLESS PERSONS. Leo G. Rigler. J.A.M.A. **137**:1501-1507, (Aug. 21), 1948.

The results of treatment of cancer of the stomach are still exceedingly poor. Of all the tumors, cancer of the stomach continues to produce by far the largest number of deaths. Most patients coming to operation, are suffering from advanced gastric cancer. Means must be devised to discover cancer of the stomach early, when the lesion is small.

In 544 symptomless persons over the age of 50, whose gastric contents showed either achlorhydria, or free hydrochloric acid of less than 30 units, three carcinomas and 19 presumably benign polypi were found by routine roentgen examination. Photofluorography has been proposed as a means of rapid screening of large numbers of persons.

St. John, Swenson and Harvey studied a series of unselected persons over the age of 50 by the fluoroscopic method alone. They found two carcinomas and one lymphosarcoma, and no polypi. In their study the author and his associates found a number of cases of enlarged rugae, resembling polypi. In the positive or doubtful cases gastroscopy was done. Rigler also found a number of hiatus hernias. Routine roentgen examination of symptomless persons is the only presently effective means for the discovery of gastric tumors in an early stage of their development.

Hyman I. Goldstein

Intestines

DIAGNOSIS AND MANAGEMENT OF REGIONAL ENTERITIS. Charles B. Puestow. Postgrad. Med. **4**:47-54, (July), 1948.

The etiology of regional enteritis is unknown. The signs and symptoms of regional enteritis vary with duration of disease and the stage in which the patient is first seen.

(1) Acute or surgical abdomen.
(2) Symptoms of ulcerative enteritis.
(3) Chronic incomplete intestinal obstruction.
(4) Chronic fistula formation and perirectal abscesses.

The diagnosis is made in the acute stage only by exploratory laparotomy. In the other stages x-ray examination reveals a stenosis of the terminal ileum. The three most important diseases to be differentiated are appendicitis, tuberculous enteritis and ulcerative colitis. At operation in the acute stage the involved segment of the small intestines may reveal only an edematous, reddened,

granular serosa. This is followed by adhesions matting several loops of small intestine together. There is always mesenteric lymphadenopathy. In the chronic stage there is obstruction with dilatation of the proximal intestine. Treatment should be conservative, but surgical complications are best treated by ileotransverse colostomy with exclusion of the ileum distal to the anastomosis.

JACOB A. RIESE

PSEUDOMYXOMA PERITONEI FROM RUPTURED MUCOCELE OF APPENDIX. D. P. Hall. South. Surgeon. **10**:264-270, (April), 1948.

There are few reported cases of pseudomyxoma of the peritoneum from appendiceal origin. Mucocele is the precursor of pseudomyxoma of the peritoneum.

Hall's patient was a man, 54 years old, complaining of severe pain in the lower abdomen with distention. The pathologist considers the condition benign histologically—but surgeons consider it potentially malignant. Pseudomyxoma peritonei may be benign, but occasionally follows a cancer-like pattern.

HYMAN I. GOLDSTEIN

NONVITAMINIC FACTORS INVOLVED IN THE PRODUCTION OF THE "SMALL INTESTINAL DEFICIENCY PATTERN". W. H. Glass. Gastroenterology. **10**:660, (April), 1948.

Glass proves that an abnormal jejunal mucosal pattern can be caused by multiple factors other than Vitamin B-complex deficiency. Abnormalities in the outlet of the stomach, which produce irregularity in the size of the bolus, produce radiographic patterns in the jejunum which are abnormal. These findings do not preclude the validity of the diagnosis of Vitamin B-complex deficiency or idiopathic steatorrhea when mechanical factors, as presented by Glass, are excluded.

In the first reported case, a duodenal spasm was apparently associated with emotional disturbance. The roentgenogram showed an advanced abnormal small intestinal pattern. The patient responded to antispasmodics and psychotherapy, not to B-complex. In the second case an organic pyloric obstruction was present. The abnormal small intestinal pattern was rectified by surgical short-circuiting. The third case was that of a duodenal ulcer with normal pattern. Following improvement of the ulcer symptoms, reexamination at the time of a Menière's seizure showed delayed gastric emptying with advanced jejunal changes. Another case had a partial obstruction of the postpyloric region and at the site of a gastroenterostomy, stoma with advanced jejunal changes. There was no response to Vitamin B-complex treatment, but subsequent subtotal gastrectomy with a well functioning stoma resulted in a normal jejunal pattern.

It is important to realize that there may be many factors involved in producing the socalled "deficiency pattern" of the small intestines.

FRANZ J. LUST

LEIOMYOSARCOMA OF THE RECTUM: REPORT OF A CASE. L. Adelson and D. Newcomb. Connecticut M. J. **12**:846, (Sept.), 1948.

Leiomyosarcoma (myosarcoma) of the large bowel is an exceedingly rare lesion. Lapeyre (1920) collected 30 cases of primary sarcoma of the rectum after a thorough survey of the literature. Of these only two were of smooth muscle origin.

Rankin and Larson (1932) reported four cases of rectal leiomyosarcoma. Bacon and Scheffler (1942) reported a case. The authors report a case in an Italian male (49 years) and give 10 references to the literature.

HYMAN I. GOLDSTEIN

THE ROLE OF THE ROENTGENOLOGIST IN THE DIAGNOSIS OF POLYPOID DISEASE OF THE COLON. Paul C. Swenson and Russell Wigh. Am. J. Roentgenol. **59**:10, (Jan.), 1948.

Roentgenograms and some pathologic reproductions together with case histories have been presented illustrating four classes of polypoid disease of the colon, namely: the single lesion, the limited but multiple type, true multiple polyposis, and the polypoid manifestations in ulcerative colitis. These cases were grouped clinically as they presented themselves to the roentgenologist. The single contrast study, the double contrast study (with stereoscopy), and the roentgenoscopically controlled compression study have all been demonstrated. Pedicles and dimpling of the bowel wall at the site of attachment of the pedicle or of the mass itself have been demonstrated and discussed in reference both to diagnostic and surgical importance. Suggestions have been made to aid in the selection of one or more methods of roentgen study.

The authors show very interesting roentgenograms of cases of nonspecific ulcerative colitis. In each case severe diarrhea and bloody stools were the chief complaints and the proctosigmoidoscopic examination revealed changes characteristic of ulcerative colitis. The roentgenograms chosen show those changes which simulate multiple polyposis. There are two principal features. One is that of islands of mucosa, either normal or edematous, which project into the bowel lumen between ulcers and although they present a polypoid appearance are merely pseudopolyps. The second feature is

actual polypoid formation, resulting from the piling up of mucosal shreds. Contributory roentgen evidence, particularly loss of haustrations and narrowing of the bowel lumen, should permit the differentiation from the familial type of multiple polyposis. FRANZ J. LUST

PATHOLOGY AND LABORATORY RESEARCH

THE EFFECT OF SMOKING CIGARETTES AND OF INTRAVENOUS ADMINISTRATION OF NICOTINE ON THE ELECTROCARDIOGRAM BASAL METABOLIC RATE, BLOOD PRESSURE, ETC. Grace M. Roth, McDonald and Charles Sheard. J.A.M.A. **125**:761-767, (July 15), 1944.

Observations by the authors on six normal persons disclosed that smoking two cigarettes decreased the cutaneous temperature in the extremities.

The basal metabolic rate was increased after smoking two cigarettes. After smoking two cigarettes consistent changes in the electrocardiogram were observed: an increased heart rate and a lowering of the amplitude of the T wave.

The authors found an increase of blood pressure and pulse rate after smoking two standard cigarettes. When nicotine was administered intravenously all the above changes noted were evident to a greater degree and occurred more rapidly. HYMAN I. GOLDSTEIN

THE EFFECT OF SMOKING ON THE VASODILATATION PRODUCED BY THE ORAL ADMINISTRATION OF 95 PER CENT ETHYL ALCOHOL OR A SUBSTANTIAL MEAL. Grace M. Roth and Charles Sheard. Am. Heart. J. **33**:654-662, (May), 1947.

The vasodilatation which follows ingestion of alcohol equivalent to 2 ounces (60 cc.) whisky, does not take place immediately but only after sufficient absorption of the alcohol has occurred. The height of vasodilatation may not be reached until fifty to sixty minutes after the ingestion of alcohol but, once the height has been reached, it persists for one to one and one-half hours.

Vasoconstriction from smoking thirty to ninety minutes after ingestion of alcohol or ingestion of food, could not be prevented by the alcohol or food at any time during vasodilatation from alcohol or food. When 30 cc. of 95 per cent ethyl-alcohol, or 2 ounces of whisky (60 cc.) are given after fasting, definite vasodilatation of the peripheral vessels occurs. Drinking a cocktail will not necessarily nullify the vasoconstricting effect of smoking. HYMAN I. GOLDSTEIN

THE EFFECT OF BLOCKADE OF THE AUTONOMIC GANGLIA IN MAN WITH TETRAETHYLAMMONIUM. R. H. Lyons et al. Am. J. M. Sc. **213**:315-323, (March), 1947.

Acheson and Moe (1945) have recently demonstrated in animals, that tetraethylammonium blocks transmission of nerve impulses through the autonomic ganglia.

The authors found that tetraethylammonium administered to man (0.2 to 0.5 mg.) intravenously or (up to 20 mg./Kg.) intramuscularly produced a series of changes which are best explained by blockade of the autonomic ganglia. There is an increase in skin temperature, postural hypotension, a fall in peripheral venous pressure and increase in heart rate and cardiac output. It produces a cessation of normal peristalsis in the gastrointestinal tract and a diminution in gastric secretion. This use has been applied clinically for the relief of pain and increased motility of the gastrointestinal tract. HYMAN I. GOLDSTEIN

TETRAETHYLAMMONIUM IN PERIPHERAL VASCULAR DISEASE AND CAUSALGIC STATES. R. L. Berry, Campbell, Lyons, Moe and Sutler. Surgery. **20**:525-535, (Oct.), 1946.

Clinical experience with tetraethylammonium bromide or chloride has shown its efficiency in producing blockade of the autonomic ganglia to a degree comparable to that obtained by the usually accepted methods of producing sympathetic block. For a number of months (8) the authors have used tetraethylammonium to produce autonomic block daily as an outpatient procedure. Following the treatment the patient is kept in the horizontal position for at least 15 to 30 minutes.

Adrenalin is specific in counteracting any untoward symptoms. The drug has been administered (August 1946) more than 1,000 times to more than 500 patients in doses with very few alarming reactions. This drug has proved satisfactory in ameliorating pain and improving the circulation, by producing sympathetic block.

The intravenous dose ranged from 100 mg. (1 cc.) to a maximum of 500 mg. (5 cc.). The injection is made slowly (about one minute).

The intramuscular injection was utilized for more prolonged effect of the autonomic blockade only in hospitalized patients with causalgic disorders, reflex sympathetic dystrophies, organic obstructive vascular lesions, including peripheral arteriosclerosis obliterans (55 patients) and thrombophlebitis (9 patients) and (18 patients) thromboangitis obliterans. HYMAN I. GOLDSTEIN

BOOK REVIEWS

TEXTBOOK OF HUMAN PHYSIOLOGY. William F. Hamilton, Ph.D., Professor of Physiology, Georgia School of Medicine. 504 pages, with 121 illustrations. F. A. Davis Co., Philadelphia, 1947. Price $6.00.

This practical textbook for medical and dental students, nurses and for busy general practitioners, presents the principals of physiology in a concise, orderly, and easily readable manner. Many medical schools have adopted this work, as the students textbook on Physiology.

The volume gives the student a condensed review of all the more essential facts concerned with human physiology.

The process of excitation, response and transmission, organization of reflex pathways, functions of the central nervous system, the sensations of taste and smell, hearing, vision, posture and equilibrium, cutaneous sensibility and pain; respiration; ventilation of the lungs; hunger, thirst, libido; action of the heart, circulation rate, blood pressure; digestion; body fluids; functions of the kidney; metabolism, and the endocrine system all receive brief, but ample consideration. This condensed textbook of physiology is recommended for the use of medical students, nurses, and busy general practitioners.

PRACTICE OF ALLERGY. Warren T. Vaughan, M.D. Second edition, thoroughly revised by J. Harvey Black, M.D., 1132 pages, illustrated. C. V. Mosby Co., St. Louis, Mo., 1948. Price $15.00.

The untimely death of Dr. Vaughan, whose ability as allergist and whose efforts to raise allergy on a level with other medical specialties, and whose writings on this subject were considered among the best, prevented revision of the first edition. Now at his demise this second edition appears under the able editorship of Dr. J. Harvey Black. I am certain that Dr. Black made every effort to retain and maintain the high standard of his valuable reference book.

Here and there one finds a particular subject that could have been elaborated on to the advantage of the reader, however, the book is well printed, the illustrations are instructive. It has a good index.

The reader will find many useful suggestions as to diagnosis and therapy.

TREATISE ON SURGICAL INFECTIONS. Frank Lamont Meleney, M.D., Associate Professor of Clinical Surgery, Columbia University. 713 pages. Oxford University Press, New York, 1948. Price $12.00.

According to the author this treatise has been in the process of preparation for the last twenty years.

There is a brief introduction by Allen O. Whipple, "to a great work". This is, indeed, a most timely volume, long needed, and now available to all those interested in surgical infections. This is the best book now in print on the subject! This treatise is the result of many years of experimental and clinical application by the author, a leader in his special field. The book has been brought right-up-to-date, including excellent discussions on the uses of Bacteriophage; Penicillin and other Antibiotics. The dyes, sulfonamides and zinc peroxide receive careful consideration by the author.

The reviewer knows of no other authoritative book on surgical infections during recent decades which so masterfully and instructively presents this all important subject, important to surgeons, medical practitioners, surgical residents and internes and to the men engaged in the several subspecialties. Dermatologists, Otolaryngologists, and plastic surgeons, too, should find this volume very helpful. The book is highly recommended as the best volume now available on this subject!

A MANUAL OF PHARMACOLOGY AND ITS APPLICATION TO THERAPEUTICS AND TOXICOLOGY. Torald Sollmann, M.D., Professor Emeritus of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Seventh Edition. 1132 pages, W. B. Saunders Company, Philadelphia and London:, 1948. Price $11.50.

As in previous editions Dr. Sollmann brought this volume up-to-date. One will find incorporated in the text material from the United States Pharmacopoeia, National Formulary and from the New and Nonofficial Remedies, which make this volume a truly comprehensive vade mecum. The medical student as well as the graduate will find many valuable and enlightening discussions, and here will learn the use he can make of the drugs and their combinations in his daily work.

Chemotherapy, antibiotics, vitamins and hormones are fully discussed. Among the newer preparations, antihistamines, curare, and the various advances made in the field of antimalarial, antimonial and antithyroid drugs, nitrogen mustard, etc. are clearly discussed.

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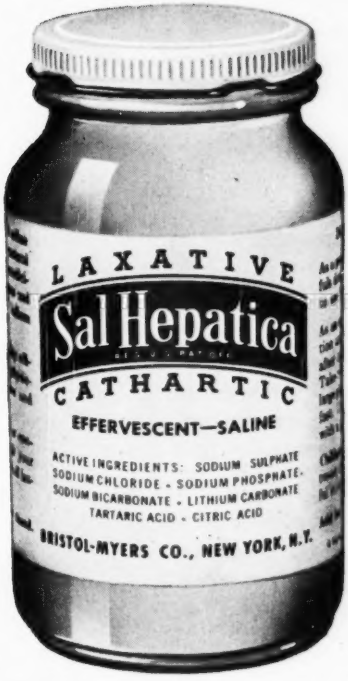

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